Guidance for Industry

Content and Format of an Abbreviated New Drug Application (ANDA) — Positron Emission Tomography (PET) Drug Products

With specific information for ANDAs for Fludeoxyglucose F18 Injection

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Draft release for comment on: April 18, 1997.

Comments and suggestions regarding this draft document should be submitted by June 28, 1997, to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm 1-23, Rockville, MD 20857. All comments should be identified with the docket number 97D-0164. For questions regarding this draft document, contact Peter Rickman, at (301) 594-0315.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

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Draft — Not for implementation

GUIDANCE FOR INDUSTRY[1]

CONTENT AND FORMAT OF AN ABBREVIATED NEW DRUG APPLICATION (ANDA) — POSITRON EMISSION TOMOGRAPHY (PET) DRUG PRODUCTS

With specific information for ANDAs for Fludeoxyglucose F18 Injection

I. INTRODUCTION

Under 21 U.S.C. 355(j), Abbreviated New Drug Applications (ANDAs) may be submitted for drug products that are the same as a listed drug. FDA's implementing regulations at 21 CFR 314.92 state that the term *same as* means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except for those uses for which approval cannot be granted because of exclusivity, or for which an existing patent may be omitted. Because a New Drug Application (NDA) for Fludeoxyglucose F18 Injection was submitted by Downstate Clinical PET Center and was approved on August 19, 1994, (NDA 20-306), ANDAs may be submitted for drug products that are the same as this reference listed drug (RLD) product.

This guidance is provided to assist applicants who wish to submit an ANDA for Fludeoxyglucose F18 Injection. The Center for Drug Evaluation and Research's *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*, provides information regarding the organization of an ANDA.

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[1]This draft guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This draft guidance represents the Agency's current thinking on the content and format of an ANDA for PET radiopharmaceutical drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, CDER, FDA, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, (Internet) http://www.fda.gov.cder/guidance.htm.

II. GENERAL INFORMATION

The content and format of abbreviated applications is described in 21 CFR 314.94. This regulation also requires the submission of three copies of the application: an archival copy, a review copy, and a field copy.[2]

An applicant should submit a complete archival (original) and review (duplicate) copy of the application that includes the following information:

A. Cover Letter

The application should include a signed and dated cover letter which includes a clear, brief introductory statement. The cover letter should be on the letterhead stationery of the applicant. The cover letter should contain the following information:

1. Purpose of the submission;

2. Type of submission (ANDA, AADA, amendment, supplement, annual report, or resubmission as a result of prior withdrawal of an application);

3. Name, title, signature, and address of the applicant;

4. Proprietary name (if any) and established name of the drug product;

5. Number of volumes submitted.

B. Letters of Authorization

1. Agent

Domestic Applicants - If a domestic firm uses an agent, a letter of authorization allowing the agent to act on behalf of the applicant should be included in the application following the cover letter.

2. Drug Master File (DMF)

[2] On March 20, 1997, FDA published a final rule (62 FR 13429) that would allow FDA to accept, under certain circumstances, electronic records and electronic signatures as equivalent to paper records and handwritten signatures executed to paper. This rule takes effect on August 20, 1997. For information on how to prepare an electronic ANDA contact the Office of Generic Drugs.

DMF letters of authorization grant the Agency the authority to refer to information in a DMF during the review of an ANDA (21 CFR 314.420). The letter of authorization should be on the DMF holder's letterhead, and dated and signed with an original signature. The letter should cite the DMF holder's name, drug name, and DMF number. If the referral is made by a third party (i.e., another corporate entity, agent, or supplier), a letter from the DMF holder should be provided giving the third party the authorization to grant referrals to the DMF. If the applicant intends to rely on DMF information concerning the bulk drug substance, authorization should be granted by the holder of the DMF for each source of bulk drug substance. This letter should be placed in the chemistry, manufacturing, and controls section along with the information submitted for the active ingredient. (See also letters dated Nov. 8, 1991, and April 8, 1994.)

If the applicant is also the manufacturer of the active ingredient, Fludeoxyglucose F18 applicants would not have to provide a DMF reference for the bulk drug substance.

C. Debarment Certification/List of Convictions

Use of a debarred individual/firm, within the meaning of 306(a) and (b) of the Federal Food, Drug and Cosmetic Act (the act) [21 U.S.C. 335a(a) and (b)], may preclude the approval of the application.

The 1992 Generic Drug Enforcement Act authorizes the FDA to debar an individual, convicted of certain crimes or found to have engaged in certain types of conduct, from providing any services to a drug product applicant. The law also authorizes the FDA to debar a firm convicted of certain crimes from obtaining or participating in certain subsequent drug approvals.

Under section 306(k)(2) of the act [21 U.S.C. 335a(k)(1)], any application for approval of a drug product submitted after June 1, 1992, must include a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)] in connection with such application. In addition to the certification requirement, section 306(k)(2) of the act [21 U.S.C. 335a(k)(2)] requires that all ANDAs and AADAs contain a conviction information statement listing any convictions the firm or its affiliated persons may have that could lead to debarment. The applicant should provide a list of any relevant convictions, the name of the person/firm convicted, the title of the section of the federal or state statute involved, the sentencing date, the court entering judgment, and

the case number, if known, and a brief description of the offense. In addition, the applicant should explain the role of each convicted person in the development of the application. The debarment certification and conviction information, which usually follows the cover letter, should be signed by a responsible officer of the applicant or by the individual responsible for signing the application. (See also letters dated July 27, 1992, Jan. 15, 1993, and April 8, 1994.)

Examples of a debarment certification and a conviction information statement follow:

Debarment Certification:

(Name of applicant) certifies that (the applicant) did not and will not use in any capacity the services of any person debarred under section 306 of the act in connection with this application.

If convictions exist for the applicant or an affiliated person responsible for the development or submission of the application that could lead to a debarment, use the following convictions statement.

Convictions Statement:

(Applicant) lists the following convictions for (applicant and/or affiliated persons):

These convictions are described in section 306(a) and (b) of the act [21 U.S.C. 335a(a) and (b)]. The list must contain all such convictions that occurred within 5 years before the date of the application (306(k)(2)).

If neither the firm nor any of its affiliated persons has convictions to list, a statement should be submitted to the effect that neither the applicant nor its affiliated persons responsible for the development or submission of the application has been convicted of a relevant offence within the last five years.

D. Field Copy Certification

The applicant must submit a certification that indicates that an accurate third copy of the technical sections (chemistry, manufacturing, and controls) of the application has been submitted to the appropriate FDA district office (see 21 CFR 314.94(d)(5) and 314.440(a)(4)). This certification should contain an original signature.

If questions arise on issues involving the submission of the third copy, please contact

the Office of Compliance in the Center for Drug Evaluation and Research at (301) 594-0054.

Example of a field copy certification follows:

(Name of applicant) certifies that the field copy is a true copy of the technical section of the application described in 21 CFR 314.94(d)(5).

III. CONTENT AND FORMAT OF AN ABBREVIATED APPLICATION

A. Application Form

Form FDA 356h should be completed, signed with an original signature, and contain the information required under 21 CFR 314.94(a)(1). The form should also list all pertinent DMFs. The applicant should identify the RLD (reference listed drug) on Form FDA 356h.

Under 21 CFR 314.50(a)(3), the applicant must submit a statement as to whether the applicant proposes to market the drug product as a prescription or over-the-counter product. If the correct box is checked on Form FDA 356h regarding prescription or over-the-counter status, no additional statement is necessary.

Each application should include a table of contents [21 CFR 314.94(a)(2)] following Form FDA 356h. For a suggested table of contents, refer to the *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*.

The table of contents helps the reviewer locate information in the application. Each section of the application should be delineated by dividers and tabbed, and the pages should be numbered sequentially.

B. Basis for Abbreviated New Drug Application Submission

The applicant must cite the name of the RLD including its dosage form and strength (21 CFR 314.94(a)(3)(i)), as identified in the publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), by the symbol "+". The product designated with the symbol "+" is the drug product selected by the Agency as the reference standard for conducting bioequivalence testing.

NDA 20-306, Fludeoxyglucose F 18 Injection USP, held by Downstate Clinical PET Center is the applicable RLD.

The ANDA product must have the same active ingredient, dosage form, strength, and route of administration as the reference listed drug product [21 CFR 314.94(a)(5)(i)(A) and 314.94(a)(6)(i)(A)]. A change from the RLD in one or more of these items requires the submission of a suitability petition to obtain permission to submit an ANDA with such change [21 CFR 314.93]. The strength of the drug product refers to the concentration or amount of active ingredient in the drug product. Generally, a change in either the concentration or total volume of a parenteral drug product will constitute a change in strength for which a suitability petition is required under 21 CFR 314.93(c).

C. Patent Certification and Exclusivity Statement

1. Patent Certification

Except as provided in 21 CFR 314.94(a)(12)(iv), the applicant must provide a certification with respect to each patent issued by the United States Patent and Trademark Office that in the opinion of the applicant and to the best of its knowledge claims the RLD or claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the act [21 U.S.C. 355(j)] and for which information is required to be filed under section 505(b) of the Act (21 U.S.C. 355(b)) and 21 CFR 314.53. As stated under this section of the Act and 21 CFR 314.94(a)(12), the applicant must provide for each patent the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

- That the patent information has not been submitted to the FDA. The applicant shall title such a certification "Paragraph I Certification."

- That the patent has expired. The applicant shall title such a certification "Paragraph II Certification."

- The date on which the patent will expire. (e.g. Patent No. _____will expire on _____.) The applicant shall title such a certification "Paragraph III Certification."

- Or, that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the drug product for which the abbreviated application is submitted. (This type of certification indicates that the applicant is challenging the patent). The applicant shall

title such a certification "Paragraph IV Certification."

A Paragraph IV certification must be accompanied by a statement that the applicant will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under 21 CFR 314.95 with respect to the content of the notice.

Under 21 CFR 314.94(a)(12)(i)(A)(1), applications for Fludeoxyglucose F 18 Injection must contain a Paragraph I certification if patent information has not been submitted to the Agency.

Example of a Paragraph I patent certification follows:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug, 21 CFR 314.94(a)(12)(ii).

A list containing patent information may be located in the Patent and Exclusivity Addendum in the Orange Book and its supplements. Patent information should be verified with the latest Orange Book edition and/or supplement.

2. Exclusivity Statement

Exclusivity is granted by the Agency for certain drug products (21 CFR 314.108). A list containing exclusivity information can be located in the Patent and Exclusivity Addendum in the Orange Book and its supplements. (See also letters dated Oct. 31, 1986, April 28, 1988, and July 29, 1988.)

A statement addressing exclusivity must be submitted even if no exclusivity exists [314.94(a)(3)(ii)].

Example where no exclusivity exists (pertaining to Fludeoxyglucose F18 Injection): According to the publication, Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) *the reference listed drug is not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the act [21 U.S.C. 355(j)(4)(D)]*.

Exclusivity information should be verified with the latest *Orange Book* edition

and/or supplement.

D. Comparison Between Generic Drug and Reference Listed Drug

1. Conditions of Use

Under CFR 314.94(a)(4), the applicant must submit a statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the RLD. The applicant is required to reference the annotated proposed labeling and the currently approved labeling for the RLD [21 CFR 314.94(a)(4)].

2. Active Ingredients

The applicant must provide a statement that the active ingredient in the proposed drug product is the same as the active ingredient in the RLD (21 CFR 314.94(a)(5)(A)). The applicant must also reference the annotated proposed labeling and the currently approved labeling for the RLD (21 CFR 314.94(a)(5)(B)).

3. Route of Administration, Dosage Form, and Strength

Under 21 CFR 314.94(a)(6), the applicant must provide a statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the RLD except for any differences that have been the subject of an approved ANDA suitability petition. The applicant should reference the annotated proposed labeling and the currently approved labeling for the RLD. If differences exist due to the approval of an ANDA suitability petition, these differences should be delineated and a copy of the approval letter for the petition should be included.

Example format follows:

The conditions of use prescribed, recommended, or suggested in the labeling proposed for the generic drug have been previously approved for the reference listed drug. [Please refer to the labeling section for a comparison of (applicant's) annotated proposed labeling and to the currently approved labeling for the reference listed drug.] The active ingredient, route of administration, dosage form, and strength are the same as the reference listed drug.

A detailed comparison of the proposed drug and the reference listed drug follows:

	Generic Drug Product	*Downstate Clinical PET Center*
Conditions of use:	*FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*	*FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*
Active ingredient:	*Fludeoxyglucose F 18*	*Fludeoxyglucose F 18*
Route of administration:	*Parenteral*	*Parenteral*
Dosage form:	*Solution*	*Solution*
Strength:	*6.8 - 35.7 mCi/mL*	*6.8 - 35.7 mCi/mL*

Under 21 CFR 314.93, a change from the RLD in strength, dosage form, or route of administration requires the submission of a suitability petition to obtain permission to file an ANDA with such a change. According to the Orange Book, the strength of the RLD for Fludeoxyglucose F18 ([^{18}F]FDG) Injection is 6.8 - 35.7 mCi/mL. The labeling of the drug product states that it contains 296 ± 3 mL of isotonic saline. Any change that affects the amount of the active ingredient or the concentration of the drug product (in mCi/mL) will be deemed to be a change in strength that, under 21 CFR 314.93, requires a suitability petition prior to filing the ANDA. Therefore, the use of a higher energy cyclotron may result in a more concentrated drug product for which a suitability petition is required under 21 CFR 314.93. In addition, a change in the total volume, and/or the amount of active ingredient, may result in a change of strength for which 21 CFR 314.93 requires a suitability petition.

E. Labeling

Refer to the *Fludeoxyglucose F18 Injection Labeling Guidance* and the Aug. 4, 1993, letter.

A side-by-side comparison of the container labels and package insert with all differences annotated and explained for the RLD and the proposed drug product must be submitted in addition to the four copies of draft (or 12 copies of final printed)

labeling (21 CFR 314.94(a)(8)).

F. Bioavailability and Bioequivalence

The applicant is required to provide information that shows that the drug product is bioequivalent to the RLD product upon which the applicant relies (21 CFR 314.94(a)(7)). (See also 21 CFR 314.94(a)(9)(ii) and (iii) and 21 CFR 320.22(b)(1).)

Any qualitative or quantitative differences in formulation from the RLD for parenteral drug products should be characterized and explained. A side-by-side comparison of the formulation of the proposed product and the RLD should be submitted. Analytical information and a physicochemical comparison should be included. Parenteral drug products may only differ in preservative, buffer, or anti-oxidant. If other changes are made in a parenteral drug product, an in vivo bioequivalence study may be needed.

Inactive ingredients used in the proposed generic drug product should have been previously approved in another drug product given by the same route of administration. The use of an approved inactive ingredient can be verified in the *Inactive Ingredient Guide*. The quantities of the inactive ingredient should not exceed the *Inactive Ingredient Guide* range. (Also refer to the *Interim Inactive Ingredients Policy* for information regarding exception and nonexception excipients.)

A waiver of evidence of in vivo bioequivalence may be requested for Fludeoxyglucose F 18 Injection. For certain drug products, such as Fludeoxyglucose F18 injection (abbreviated as [^{18}F]FDG), the in vivo bioequivalence may be self-evident. The FDA will waive the requirement for the submission of evidence obtained in vivo demonstrating bioequivalence if FDA determines that in vivo bioequivalence is self-evident. For example, in vivo bioequivalence may be self-evident if the drug product meets the following criteria:

- The drug product is a parenteral solution intended solely for administration by injection.

- The drug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application [21 CFR 320.22(b)].

Example of request for waiver of evidence of in vivo bioequivalence:

The (applicant) requests that the FDA waive the requirement for the submission of evidence demonstrating in vivo bioequivalence for (the proposed drug product). The

(drug product) meets the provisions of 21 CFR 320.22(b)(1)(i) and (ii).

In addition, under 21 CFR 320.22(e), for good cause, FDA may waive a requirement for submission of evidence of in vivo bioavailability if FDA determines that a waiver is compatible with the protection of the public health.

G. Components and Composition

Components (active and inactive ingredients) and composition of the drug product should be included. For Fludeoxyglucose F18 Injection, the active ingredient (drug substance) is Fludeoxyglucose F 18 (2-deoxy-2-[^{18}F]fluoro-D-glucose).

All inactive ingredients should be identified by their chemical names and their quantity and/or concentration (e.g., mg/mL) should be included. Applicants should refer to 21 CFR 314.94(a)(9)(iii) concerning the inactive ingredient changes permitted in a generic drug product intended for parenteral use. If inactive ingredients in the proposed product differ qualitatively and/or quantitatively from the RLD, information should be provided to demonstrate that the difference does not affect the safety of the proposed drug product. The submitted information should include, but need not be limited to, the following: (1) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and are within the same concentration range, (2) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (3) a comparison of the physical and chemical properties (e.g., pH, osmolarity, toxicity) of the proposed drug product with that of the RLD, and (4) information to show that the inactive ingredients do not affect these properties.

For [^{18}F]FDG, the Agency recognizes that the drug product formulated at the end of the synthesis (i.e., a batch) may be used as a single dose or as multiple doses. The quantitative composition of the unit dose may be assumed to be the same as that of the entire batch.

H. Raw Materials Controls

Information concerning the raw materials used for the manufacture of [^{18}F]FDG may be provided in the following format:

1. Components

    a. Name and Full Address(es) of the Supplier.

b. Method of Purification

If a component (e.g., mannose triflate, kryptofix) as received from its supplier is further purified or recrystallized, full information on this process, including the rationale, the method(s), and the solvents employed (if any) should be included in the application.

c. Specifications and Analytical Test Methods

For each component and inactive ingredient, the following information should be included:

i. The applicant should provide specifications and a test method for the identity of all components. The identity test should be performed prior to release of each lot of the material. Details of the analytical test method should be included in the application.

ii. If the suppliers of the raw materials are different than those listed in the RLD, then the suppliers should be validated. All raw material components should have acceptance specifications and be accepted with a certificate of analysis (COA). Full testing to determine the accuracy of the COA should be preformed. The supplier of the raw materials should be in compliance with Current Good Manufacturing Practice (CGMP) regulations. Once a supplier is validated, and a manufacturer wants to change suppliers, then the application should include data which demonstrates that the [^{18}F]FDG produced from raw materials from a new supplier are equivalent to the current supplier in terms of conformance with established specifications.

d. Retest Schedule

Each raw material should be retested periodically to determine that it still meets specifications. The periodic retest schedule should be provided.

2. Inactive Ingredients

For each inactive ingredient used in the drug product formulation, a statement

of its quality [e.g., American Chemical Society (ACS), United States Pharmacopeia (USP), National Formulary (NF)] should be provided. A certificate of analysis from a validated supplier that includes specifications and test results may be used to accept this material.

3. All Other Components (e.g. reagents, solvents)

A list of all other components which are used in the synthesis and purification of the drug product (e.g., all reactants, chemicals, solvents, reagents, that were not included above) should be included. A statement of the quality [e.g., American Chemical Society (ACS), United States Pharmacopeia (USP), National Formulary (NF)] of each component should be provided. A certificate of analysis, from a validated supplier, that includes specifications and test results may be used to accept this material.

4. Reference Standard

For [^{18}F] FDG, 2-deoxy-2-fluoro-D-glucose, a nonradioactive reference standard is used to establish and/or to verify the identity of Fludeoxyglucose F18 in the drug product. It also may be used for the determination of specific activity. The following information should be provided:

a. Source

Name and address of the supplier. If the reference standard is synthesized in-house, a statement to this effect should be included.

b. Proof of Identity

If the reference standard is purchased commercially, the applicant should include the certificate of analysis from its supplier. If the material is synthesized in-house, representative data to establish unequivocally the identity of the reference material lot as 2-deoxy-2-fluoro-D-glucose should be provided. The documentation should include complete spectrophotometric data, other applicable analytical data, as well as information on the synthetic route used.

I. Description of Manufacturing Facility

The following information should be provided (see also 21 CFR parts 210 and 211):

1. Name and full address(es) of the facility(ies) [including building and room numbers] used in manufacturing, packaging, release testing, and stability testing of the drug product. Please include the Registration Number of the facility.

2. Certification that the facility is in compliance with the Current Good Manufacturing Practices (CGMPs) (see also letter of Oct. 14, 1994, on field/headquarters agreement). The applicant and any contract facilities should provide the following statement with an original signature.

(Name of Applicant) certifies that the methods used in and the facilities and controls used for the manufacturing, processing, packaging, testing, and holding of (product) conform, and will continue to conform, to the Current Good Manufacturing Practice regulations under 21 CFR parts 210 and 211.

J. Outside Firms Including Contract Testing Laboratories

The following information should be provided:

1. Name and full address of each facility. Please include the Registration Number.

2. The function(s) of each facility.

3. A certification that the facility is in compliance with the CGMPs.

K. Manufacturing and Processing Instructions

1. Manufacture of Drug Substance

The following information should be submitted:

a. Batch Formula

The batch formula for the test batch(es) (e.g., the batch used in support of the application) and the proposed production batches should be included. A complete list of all the ingredients (whether or not they remain in the finished product) and their amounts used in the batch formulation should be provided.

b. Production of the Radionuclide

i. Description of the Particle Accelerator

A brief description of the particle accelerator including its make and model should be provided. Applicants should note that the validation information on the accelerator demonstrating that the equipment is capable of consistently operating within the established limits and tolerances should be available on site for inspection.

ii. Operating Parameters

Operating parameters for the production at the manufacturing site should be defined. Examples of the operating parameters that should be included are maximum particle energy, beam current, and irradiation (bombardment) times. The value(s) or range of values for each defined operating parameter should be included in the application.

iii. Target Body

Specifications for the target body and the foil(s) which come in contact with the target material should be provided. These should include the composition of the target body and foil materials and the volume of the target. Information should be provided on procedures which are used to establish equivalency when an existing target body and/or foil(s) are replaced.

iv. Recycling of Oxygen-18 Enriched Water

If oxygen-18 [^{18}O]water is not recycled, this fact should be so stated. If it is recycled, procedures used for its reprocessing should be described. Information should be provided to demonstrate that the recycling and/or reprocessing of [^{18}O]water does not change the drug product quality impurity profile.

c. Synthesis and Purification of Drug Substance

i. Description of Radiochemical Synthesis and Purification Equipment

The equipment used for the synthesis and purification of

Fludeoxyglucose F18 should be described. It should include a schematic flow diagram of the equipment from the target to the vial filling unit. A description of various components (e.g., tubing, reaction vessel, columns, and the function of each purification component (e.g., various columns) should be included. The components that are replaced after each manufacturing operation, and the components that are replaced periodically should be identified. Suppliers for each of the replaceable components (e.g., various purification columns and filter) should be provided. The procedures used in the assembly of components should be described.

ii. Description of Radiochemical Synthesis and Purification Operation

Identify the components and the processes that are under computer control and the ones that are under manual control. Applicants should note that the validation information demonstrating that the equipment is capable of consistently operating within the established limits and tolerances should be available on site for inspection.

A stepwise description of the radiochemical synthesis and purification operation, including in-process controls (refer to section L.), should be provided. An acceptable range of yields of the radioactivity for the drug product should also be provided. The proposed range of yields should be justified.

iii. Post Synthesis Operations

A description of how the synthesis and purification equipment is prepared for a subsequent batch should be provided. All cleaning and purging procedures should be fully described.

2. Manufacture of Drug Product

a. Production Operations

The procedures used in the manufacture of the drug product should be described.

b. Reprocessing of the Drug Product

A drug product batch should not be reprocessed unless the reprocessing procedures and conditions have been approved in the ANDA. If an applicant intends to reprocess a drug product batch, the conditions (circumstances) and full reprocessing procedures should be submitted.

c. Proposed Master Production Records [21 CFR 314.94(a)(9)(i)]:

A copy of the blank master production record, including a description of the equipment, to be used for the manufacture of a lot of the drug product should be included.

3. Microbiological Validation

a. Introduction

i. Purpose

The recommendations in this document apply to ANDAs for sterile [^{18}F]FDG. These recommendations also apply to approved applications when supplements associated with sterile processing are submitted.

ii. Documenting Sterilization Process Validation

Sterilization process validation data should be generated using procedures and conditions that are fully representative and descriptive of the procedures and conditions proposed for manufacture of the product in the application.

The Center recognizes that for most [^{18}F]FDG products, the final drug product will be manufactured using aseptic techniques rather than terminal sterilization. The Center also recognizes that conventional methods for the validation of aseptic processes may not apply to the validation of the sterile production of [^{18}F]FDG due to the very small number of product units manufactured from a batch or lot, and its short half-life.

Technical subsections of an application are often reviewed apart from the main body of the application. For this reason, it is

recommended that the microbiology subsection include an introductory description of the drug product (syringe, vial, glass, plastic, closure system) and the product's intended use. It is further recommended that the information describing sterilization processes be filed in a subsection (or volume) of the chemistry manufacturing, and controls (CMC) portion of an application. This permits the CMC subsections to be reviewed simultaneously by different reviewers in different locations.

b. Information for Terminal Moist Heat Sterilization Processes

It is not expected that FDG-F18 products will be sterilized by terminal moist heat processes. Information relating to aseptic processing for the manufacture of FDG-F18 drug products is provided under "Information for Aseptic Fill Manufacturing Processes" (section c.). However, should FDG-F18 be sterilized by terminal moist heat methods, information should be submitted in support of sterility assurance as described in Section II of the *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

c. Information for Aseptic Fill Manufacturing Processes

The following types of information should be submitted in support of sterility assurance for FDG-F18 manufactured by aseptic processing. The finished drug product should be described including the product solution (i.e., composition and pH) and the container-closure system(s) to be sterilized including size(s), fill volume, or secondary packaging. The route of product administration and the range of product dosage should be provided.

i. Buildings and Facilities

A brief description of the manufacturing building and aseptic facilities should be provided. The following information should be included.

- Floor Plan - A floor plan of the area(s) housing the aseptic filling facilities including preparation areas should be provided. The air cleanliness class of each area should be identified (e.g., Class 100, Class 10,000, Class

100,000). Isolators or barrier systems should be identified.

- Location of equipment - The placement of all critical equipment including, but not limited to, laminar flow hoods, autoclaves, and filling devices should be identified. Equipment within barrier or isolation systems should be noted.

ii. Overall Manufacturing Operation

The overall manufacturing operation including, for example, solution compounding, component preparation, filling, capping, and aseptic assembly should be described. The normal flow (movement) of product and components from formulation to finished dosage form should be identified and indicated on (or in relation to) the floor plan described above. The following information should be considered when describing the overall manufacturing operation.

- Drug Product Solution Filtration - The specific bulk drug product solution filtration processes, including the use of tandem filter units, prefilters, and bacterial retentive filters should be described. A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product. For simple aqueous solutions, a certification from the filter manufacturer is often adequate. Effects of the filter on the product formulation should be described (e.g., adsorption of preservatives or active drug substance, or extractables).

- Specifications Concerning Holding Periods - 21 CFR 211.111 requires the establishment of appropriate time limits for completing each phase of production to ensure the quality of the drug product. Therefore, specifications concerning any holding periods between the compounding of the bulk drug product and its filling into final containers should be provided. These specifications should include, for example, times, temperatures,

conditions of storage. Procedures used to protect microbiological quality of the bulk drug or components during these holding periods should be indicated. Maintenance of the microbiological quality during holding periods may need verification. These technical burdens may be reduced if components of the drug solution are prepared fresh each day and maintained sterile prior to compounding.

- Critical Operations - The critical operations that expose product or product contact surfaces to the environment (such as transfer of sterilized containers or closures to the aseptic filling areas) should be described. Any barrier or isolation systems should be described.

iii. Sterilization and Depyrogenation of Containers, Closures, Equipment, and Components

The sterilization and depyrogenation processes used for containers, closures, equipment, components, and barrier systems should be described. A description of the methods for validation of these processes should be provided including, where applicable, heat distribution, and penetration summaries, biological challenge studies (microbiological indicators and endotoxin), and routine monitoring procedures. Data (including controls) demonstrating distribution and penetration of the sterilant and microbiological efficacy of each process should be submitted. For applicants using drug product containers which are purchased sterile from a vendor, a certificate from the vendor may be provided to substitute for the above information.

- Bulk Drug Solution Components That are Sterilized Separately - If the bulk drug solution is aseptically formulated from components that are sterilized separately, information and data concerning the validation of each of these separate sterilization processes should be provided.

- Sterilization Information in the Batch Records - The batch record supplied with the chemistry, manufacturing, and controls section of the application should identify the validated process(es) to be used for sterilization or

depyrogenation of any container-closure components. This information may be included in the batch record by reference to the validation protocol or standard operating procedure (SOP), or by reference to the vendor certificate for drug product containers purchased sterile from a vendor.

iv. Procedures and Specifications for Media Fills

Media fills are simulated manufacturing operations using microbiological growth medium in place of drug product. The procedures and specifications used for media fills, and summaries of results for validation using the same container-closure system and filling process that is to be used for the product should be described. The microbiological testing method(s) used should be described. Any procedural deviations between the media fill and the production process should be indicated. A summary of recent media fill results (usually for at least 3 successful trials), including failures, should be provided.

v. Actions Concerning Product When Media Fills Fail

Descriptions of investigation plans and appropriate corrective actions should be provided.

vi. Microbiological Monitoring of the Environment

The microbiological monitoring program used during routine production and media fills should be described. The frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded should be included.

- Exceeded Limits - A description of the actions taken when environmental microbiological specifications are exceeded should be provided.

vii. Container-Closure and Package Integrity

The methods and results demonstrating the integrity of the microbiological barrier of the container-closure system should be

summarized. This should include testing for initial validation. For initial validation of microbiological integrity of container-closure systems, product sterility testing is not normally considered sufficient.

viii. Test Methods and Release Criteria

Product release tests for injectable products include sterility and pyrogenicity (or endotoxins) assessments as prescribed in 21 CFR 211.167(a). However, 21 CFR 211.165(a) permits the release of batches of drug composed of short-lived radiopharmaceuticals prior to the completion of sterility and pyrogen testing, but requires that such testing of each batch be started "as soon as possible." The laboratories performing these tests (particularly contract laboratories) should be identified and these should be in compliance with CGMP requirements.

- Sterility Test - Sterility test methods for [^{18}F]FDG will usually differ significantly from compendial test methods, so a clear description of the test should be provided. Procedures should be described and include the protocol for the selection of samples for testing. Testing performed within barrier systems should be discussed, and information concerning validation of the barrier system may be necessary.

- Bacterial Endotoxins Test and Method - Describe the bacterial endotoxins test for the product. This description should include qualification of the laboratory, inhibition, and enhancement testing and results, determination of noninhibitory concentration and maximum valid dilution. For further information see the agency guidance entitled *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*.

ix. Evidence of Formal Written Procedures

Evidence should be provided that there are formal, written procedures describing the above elements. Such evidence may

consist of standard operating procedures (SOPs), or a listing of SOPs or protocols submitted as part of the elements listed above.

d. Maintenance of Microbiological Control and Quality: Stability Considerations

Due to the extremely short period of use for FDG-F18, stability considerations with regard to microbiological quality are greatly abbreviated.

L. In-Process Controls

1. In-Process Controls

A description of any in-process controls should be provided. Examples of procedures that may be performed are the yields of fluoride ions (in mCi), temperature of the reaction vessel, gas pressure and/or flow rate, and synthesis time. In certain automated units, it may not be possible to directly monitor certain in-process parameters. In this case, it should be so stated.

2. Copy of Executed Batch Record

An executed batch record for a representative batch should be submitted. The following information should be included in accordance with 21 CFR 314.50(d)(1)(ii)(b):

- The specifications and test procedures for each component and for the drug product;
- Names and addresses of all facilities involved in manufacturing, processing, packaging, and testing of the drug product and identification of the operation performed by each facility;
- The name and address of the supplier of the container/closure system;
- The results (primary data) of any tests performed on the components of the drug product, as required by 21 CFR 211.165.

Applicants should note that although records for other batches (validation and/or stability) used to support the application, need not be included in the submission, additional information on these may be requested during the review process. Batch records for all the batches used to support the application should be available on site for inspection.

M. Labeling Procedures

The procedure for labeling of the drug product should be described.

N. Container

The following information regarding the container/closure should be provided:

- Name and full address of the manufacturer of the container/closure system or individual components. Appropriate DMF reference(s), if any, and the letter(s) of authorization (LOA) should be included in the ANDA;
- Container glass type (refer to USP chapter < 661 >); Composition of the stopper and crimp seal (e.g., aluminum);
- Physical description (e.g., size, shape, volume, product catalog number);
- Container/closure compatibility, including leaching
- Acceptance specifications and tests performed.

O. Controls for the Finished Dosage Form

For general information on controls for the drug product, refer to the *Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products*

1. Sampling Procedures

If multiple vials are manufactured, a sampling plan should be provided to assure that the test sample of the drug product is representative of the entire batch. However, if only one vial is manufactured, the description of the sampling procedure should be limited to the amount (volume) that is withdrawn from the final container and how it is distributed among the individual tests.

2. Regulatory Specifications, Methods, and Testing Schedules

The application should provide a list of specifications and identify the test methods (by name and code number) used to control the identity, strength, quality, and purity of the drug product. A schedule for performing each proposed test (i.e., pre or post release, frequency of testing) should be included. For [^{18}F]FDG, applicants should refer to section P "Analytical Methods" below for a list of tests that may satisfy the relevant identity, strength, quality, and purity criteria.

P. Analytical Methods

In this section, full details of the analytical test methods should be provided. The following is a list of tests and schedules which, in the current opinion of the Agency, satisfy the identity, strength, quality, and purity criteria for the drug product.

1. Appearance

The test method and specifications for the appearance of the drug product should provide insurance that the drug product is clear, colorless, and free of particulate matter. This may be accomplished by visualization of the drug product through leaded glass. If, due to radiation safety considerations, the ability to visually inspect [^{18}F]FDG is limited, one acceptable approach is to incorporate procedures to provide that: (1) each component or container-closure system is inspected individually for visual evidence of particulate, foreign matter, and container-closure defects immediately before use; (2) defective components will not be used; and (3) the batch production and control record of the [^{18}F]FDG includes a signed or initialed verification that such inspection was conducted and that only acceptable finished articles were used.

2. Identity Tests(s)

Test methods and specifications for the radionuclidic and radiochemical identity of the drug product should be described.

a. Radionuclidic

The radionuclidic identity should be established on every batch of the drug product by the method described in the USP monograph for Fludeoxyglucose F18 Injection.

b. Radiochemical

The radiochemical identity may be established by a chromatographic procedure by comparing the radioactive drug product with the well characterized nonradioactive 2-deoxy-2-fluoro-D-glucose reference standard in a procedure such as HPLC or TLC. The radiochemical identity test should be performed on every batch of the drug product prior to its release.

3. Assay (Radioconcentration)

Specifications (range), in mCi/mL, and the method of determination of radioconcentration of the drug product should be described. The method should clearly describe the procedure used for the determination of total radioactivity and the procedure used for the determination of the final volume in the container. This test should be performed on every batch of the drug product prior to its release.

4. Specific Activity

For [^{18}F]FDG, if a no-carrier added synthetic route is used, the specific activity need not be determined on a routine basis provided it is validated. Validation requires that the applicant of provide a drug product with consistent specific activity that at least meets the USP monograph requirements.

5. Purity

a. Radiochemical Purity

Specification and test method(s) for the radiochemical purity of the drug product should be described. A test method based on USP Fludeoxyglucose F18 Injection monograph may be acceptable. The radiochemical purity test method should be specific for Fludeoxyglucose F18. Applicants should demonstrate that the radioactivity associated with potential radiochemical impurities does not interfere with the measurement of radioactivity peak associated with Fludeoxyglucose F18. The radiochemical purity test should be performed on every batch of the drug product prior to its release.

b. Stereoisomeric Purity

In synthetic methods, where there is a possibility of formation of a stereoisomeric impurity (e.g., contamination of α and β anomers of fluorodeoxymannose in the electrophilic substitution synthesis method), a specification and a test method for the stereoisomeric purity should be provided. The drug product should meet the USP Fludeoxyglucose F18 Injection monograph for stereoisomeric purity requirements.

c. Radionuclidic Purity

Specifications for the radionuclidic purity and method for its determination should be described. The test method described in the

USP monograph may be used. With acceptable validation, the radionuclidic purity test may be performed after release of the drug product on the day of manufacture.

d. Chemical Purity

This drug product may be manufactured using different synthetic routes and processes and, therefore, may contain different impurities. Specifications, suitable methods, and schedules of testing for each impurity should be provided in the application. For example, if an applicant uses the Fludeoxyglucose F18 synthesis described by Hamacher et.al. [J. Nucl. Med. 27, 235-238 (1986)], then the residual amounts of kryptofix and the organic solvents employed in its manufacture may need to be monitored prior to the release of every batch of the drug product. Levels of other chemical impurities that may be found in the drug product (e.g., 2-chloro-2-deoxy-D-glucose) should be determined.

6. Pharmaceutical Quality

a. pH

A specification and the method of determination of pH of the drug product should be provided. The pH test should be performed prior to the release of every batch of the drug product. A pH paper test method may be acceptable, if performed using the reference standards at the lower and the upper range (with some allowance for the inaccuracy of the method) of the specifications. Applicants should note that during the shelf life, the pH of the drug product must remain within the proposed limits.

b. Osmolarity

Applicants should provide information that [^{18}F]FDG will yield a reproducible osmolarity.

c. Membrane Filter Integrity Test

The integrity of the membrane filter used to sterilize the radiochemical product should be assessed prior to the release of the drug product. The test method and specifications should be provided in the application.

The bubble point measurement method may be used to test the membrane filter integrity.

d. Bacterial Endotoxin Testing

The test should be performed on every batch.

e. Sterility Testing

The test should be performed on every batch.

7. Method Validation

The applicant should only submit those methods in the method validation package that are non USP methods.

Q. Stability of Finished Dosage Form[3]

1. Selection and Number of Batches

Where a 60 minute irradiation time is employed, a single stability batch will suffice. Where a range of irradiation times are employed, three additional batches of the drug product manufactured at the upper end should be studied.

2. Proposed Expiration Dating Period

An expiration dating period for the drug product, based on its stability, should be proposed in the application. The drug product should meet all specifications at expiry.

3. Test Procedures

Full testing should be performed at the initial time point (i.e., at release) and at the expiry period. Because of the short expiration dating period, the sterility and bacterial endotoxin testing need only be performed at release.

4. Storage Conditions

[3] The ICH Q1A guideline, *Stability Testing of New Drug Substances and Products*, and the *Guideline for Submitting Documentation For the Stability of Human Drugs and Biologics*(Stability Guidance) provide broad guidance in designing the stability studies for drug products.

Stability studies should be performed in the same container/closure system and at the same temperature in which the drug product will be stored during its shelf life (e.g., the drug product vial). The vial should be stored in the inverted position during the stability study.

5. Analytical Results on Stability Batch

The stability study analytical results should be provided in the application. Relevant information should include batch number, date of manufacture, storage condition, vial position, total radioactivity, and radioconcentration.

6. Postapproval Stability Protocol

The first three production batches are to be placed on the stability protocol. After the marketing approval of an ANDA, one production batch per year should be placed on the stability protocol.

R. Samples

If the analytical methods are to be validated in FDA laboratories, the applicant will be notified when samples should be provided. See also 21 CFR 314.94(a)(10) and 21 CFR 314.50(e)(1) and (e)(2)(i).

S. Other Information

Copies of cited references, their English translation (if not in English), and letters of authorization must be included as part of the other information in the application (21 CFR 314.50(g)(1) and (2)).

IV. REFERENCES[4]

Letters to Industry

October 31, 1986, letter to all NDA and ANDA holders and applicants on patent issues and the three-year exclusivity provisions.

[4]The reference documents are available from the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; (tel) 301-827-4573.

April 28, 1988, letter from the Director, Center for Drug Evaluation and Research, to all NDA and ANDA holders and applicants on the Drug Price Competition and Patent Term Restoration Act of 1984. The letter focuses on the three- and five-year exclusivity provisions.

July 29, 1988, letter from the Director, Center for Drug Evaluation and Research, to industry on the Drug Price Competition and Patent Term Restoration Act of 1984.

November 8, 1991, letter from the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to industry on improving the efficiency and effectiveness of the generic drug review process.

July 27, 1992, letter from the Deputy Commissioner for Operations to drug manufacturers/industry associations on the 1992 Generic Drug Enforcement Act, specifically on debarment certification and convictions statements.

January 15, 1993, letter from the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to all ANDA and AADA applicants regarding refusal to file and refusal to approve incomplete applications based on the new requirements of the 1992 Generic Drug Enforcement Act.

August 4, 1993, letter from the Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to industry providing information on labeling, scale-up, packaging, minor/major amendment criteria, and bioequivalence requirements.

April 8, 1994, letter from the Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to all ANDA and AADA applicants on a variety of application-related issues. This letter also contains a list of industry questions and Agency answers resulting from the August 4, 1993, letter to industry.

October 14, 1994, letter from the Director, Center for Drug Evaluation and Research and the Associate Commissioner for Regulatory Affairs to all NDA, ANDA, and AADA applicants on the roles of CDER chemistry review scientists and Office of Regulatory Affairs field investigators.

Guidance Documents

International Conference on Harmonisation. 1994. *Stability Testing of New Drug Substances and Products*, ICH-Q1A, September 1994.

U.S. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) and Center for Veterinary Medicine (CVM). 1994. *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, November 1994.

DHHS, FDA. 1987. *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*, February 1987.

DHHS, FDA. 1987. *Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products*, February 1987.

DHHS, FDA, CDER. *Approved Drug Products With Therapeutic Equivalence Evaluations*.

DHHS, FDA, CDER, Office of Compliance. 1987. *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices,* November 1987.

DHHS, FDA, CDER, Office of Generic Drugs. 1997. *Fludeoxyglucose F18 Injection Labeling Guidance*, January 1997.

DHHS, FDA, CDER, Office of Generic Drugs. 1994. *Interim Inactive Ingredients Policy*, November 17, 1994.

DHHS, FDA, CDER, Office of Management. *Inactive Ingredient Guide*.

DHHS, FDA, CDER. 1997. *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*, April 1997.

Guidance for Industry

Content and Format of an Abbreviated New Drug Application (ANDA) — Positron Emission Tomography (PET) Drug Products

With specific information for ANDAs for Fludeoxyglucose F18 Injection

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Draft release for comment on: April 18, 1997.

Comments and suggestions regarding this draft document should be submitted by June 28, 1997, to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm 1-23, Rockville, MD 20857. All comments should be identified with the docket number 97D-0164. For questions regarding this draft document, contact Peter Rickman, at (301) 594-0315.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

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Draft — Not for implementation

GUIDANCE FOR INDUSTRY[1]

CONTENT AND FORMAT OF AN ABBREVIATED NEW DRUG APPLICATION (ANDA) — POSITRON EMISSION TOMOGRAPHY (PET) DRUG PRODUCTS

With specific information for ANDAs for Fludeoxyglucose F18 Injection

I. INTRODUCTION

Under 21 U.S.C. 355(j), Abbreviated New Drug Applications (ANDAs) may be submitted for drug products that are the same as a listed drug. FDA's implementing regulations at 21 CFR 314.92 state that the term *same as* means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except for those uses for which approval cannot be granted because of exclusivity, or for which an existing patent may be omitted. Because a New Drug Application (NDA) for Fludeoxyglucose F18 Injection was submitted by Downstate Clinical PET Center and was approved on August 19, 1994, (NDA 20-306), ANDAs may be submitted for drug products that are the same as this reference listed drug (RLD) product.

This guidance is provided to assist applicants who wish to submit an ANDA for Fludeoxyglucose F18 Injection. The Center for Drug Evaluation and Research's *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*, provides information regarding the organization of an ANDA.

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[1]This draft guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This draft guidance represents the Agency's current thinking on the content and format of an ANDA for PET radiopharmaceutical drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, CDER, FDA, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, (Internet) http://www.fda.gov.cder/guidance.htm.

II. GENERAL INFORMATION

The content and format of abbreviated applications is described in 21 CFR 314.94. This regulation also requires the submission of three copies of the application: an archival copy, a review copy, and a field copy.[2]

An applicant should submit a complete archival (original) and review (duplicate) copy of the application that includes the following information:

A. Cover Letter

The application should include a signed and dated cover letter which includes a clear, brief introductory statement. The cover letter should be on the letterhead stationery of the applicant. The cover letter should contain the following information:

1. Purpose of the submission;

2. Type of submission (ANDA, AADA, amendment, supplement, annual report, or resubmission as a result of prior withdrawal of an application);

3. Name, title, signature, and address of the applicant;

4. Proprietary name (if any) and established name of the drug product;

5. Number of volumes submitted.

B. Letters of Authorization

1. Agent

Domestic Applicants - If a domestic firm uses an agent, a letter of authorization allowing the agent to act on behalf of the applicant should be included in the application following the cover letter.

2. Drug Master File (DMF)

[2] On March 20, 1997, FDA published a final rule (62 FR 13429) that would allow FDA to accept, under certain circumstances, electronic records and electronic signatures as equivalent to paper records and handwritten signatures executed to paper. This rule takes effect on August 20, 1997. For information on how to prepare an electronic ANDA contact the Office of Generic Drugs.

DMF letters of authorization grant the Agency the authority to refer to information in a DMF during the review of an ANDA (21 CFR 314.420). The letter of authorization should be on the DMF holder's letterhead, and dated and signed with an original signature. The letter should cite the DMF holder's name, drug name, and DMF number. If the referral is made by a third party (i.e., another corporate entity, agent, or supplier), a letter from the DMF holder should be provided giving the third party the authorization to grant referrals to the DMF. If the applicant intends to rely on DMF information concerning the bulk drug substance, authorization should be granted by the holder of the DMF for each source of bulk drug substance. This letter should be placed in the chemistry, manufacturing, and controls section along with the information submitted for the active ingredient. (See also letters dated Nov. 8, 1991, and April 8, 1994.)

If the applicant is also the manufacturer of the active ingredient, Fludeoxyglucose F18 applicants would not have to provide a DMF reference for the bulk drug substance.

C. Debarment Certification/List of Convictions

Use of a debarred individual/firm, within the meaning of 306(a) and (b) of the Federal Food, Drug and Cosmetic Act (the act) [21 U.S.C. 335a(a) and (b)], may preclude the approval of the application.

The 1992 Generic Drug Enforcement Act authorizes the FDA to debar an individual, convicted of certain crimes or found to have engaged in certain types of conduct, from providing any services to a drug product applicant. The law also authorizes the FDA to debar a firm convicted of certain crimes from obtaining or participating in certain subsequent drug approvals.

Under section 306(k)(2) of the act [21 U.S.C. 335a(k)(1)], any application for approval of a drug product submitted after June 1, 1992, must include a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)] in connection with such application. In addition to the certification requirement, section 306(k)(2) of the act [21 U.S.C. 335a(k)(2)] requires that all ANDAs and AADAs contain a conviction information statement listing any convictions the firm or its affiliated persons may have that could lead to debarment. The applicant should provide a list of any relevant convictions, the name of the person/firm convicted, the title of the section of the federal or state statute involved, the sentencing date, the court entering judgment, and

the case number, if known, and a brief description of the offense. In addition, the applicant should explain the role of each convicted person in the development of the application. The debarment certification and conviction information, which usually follows the cover letter, should be signed by a responsible officer of the applicant or by the individual responsible for signing the application. (See also letters dated July 27, 1992, Jan. 15, 1993, and April 8, 1994.)

Examples of a debarment certification and a conviction information statement follow:

Debarment Certification:

(Name of applicant) certifies that (the applicant) did not and will not use in any capacity the services of any person debarred under section 306 of the act in connection with this application.

If convictions exist for the applicant or an affiliated person responsible for the development or submission of the application that could lead to a debarment, use the following convictions statement.

Convictions Statement:

(Applicant) lists the following convictions for (applicant and/or affiliated persons):

These convictions are described in section 306(a) and (b) of the act [21 U.S.C. 335a(a) and (b)]. The list must contain all such convictions that occurred within 5 years before the date of the application (306(k)(2)).

If neither the firm nor any of its affiliated persons has convictions to list, a statement should be submitted to the effect that neither the applicant nor its affiliated persons responsible for the development or submission of the application has been convicted of a relevant offence within the last five years.

D. Field Copy Certification

The applicant must submit a certification that indicates that an accurate third copy of the technical sections (chemistry, manufacturing, and controls) of the application has been submitted to the appropriate FDA district office (see 21 CFR 314.94(d)(5) and 314.440(a)(4)). This certification should contain an original signature.

If questions arise on issues involving the submission of the third copy, please contact

the Office of Compliance in the Center for Drug Evaluation and Research at (301) 594-0054.

Example of a field copy certification follows:

(Name of applicant) certifies that the field copy is a true copy of the technical section of the application described in 21 CFR 314.94(d)(5).

III. CONTENT AND FORMAT OF AN ABBREVIATED APPLICATION

A. Application Form

Form FDA 356h should be completed, signed with an original signature, and contain the information required under 21 CFR 314.94(a)(1). The form should also list all pertinent DMFs. The applicant should identify the RLD (reference listed drug) on Form FDA 356h.

Under 21 CFR 314.50(a)(3), the applicant must submit a statement as to whether the applicant proposes to market the drug product as a prescription or over-the-counter product. If the correct box is checked on Form FDA 356h regarding prescription or over-the-counter status, no additional statement is necessary.

Each application should include a table of contents [21 CFR 314.94(a)(2)] following Form FDA 356h. For a suggested table of contents, refer to the *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*.

The table of contents helps the reviewer locate information in the application. Each section of the application should be delineated by dividers and tabbed, and the pages should be numbered sequentially.

B. Basis for Abbreviated New Drug Application Submission

The applicant must cite the name of the RLD including its dosage form and strength (21 CFR 314.94(a)(3)(i)), as identified in the publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), by the symbol "+". The product designated with the symbol "+" is the drug product selected by the Agency as the reference standard for conducting bioequivalence testing.

NDA 20-306, Fludeoxyglucose F 18 Injection USP, held by Downstate Clinical PET Center is the applicable RLD.

The ANDA product must have the same active ingredient, dosage form, strength, and route of administration as the reference listed drug product [21 CFR 314.94(a)(5)(i)(A) and 314.94(a)(6)(i)(A)]. A change from the RLD in one or more of these items requires the submission of a suitability petition to obtain permission to submit an ANDA with such change [21 CFR 314.93]. The strength of the drug product refers to the concentration or amount of active ingredient in the drug product. Generally, a change in either the concentration or total volume of a parenteral drug product will constitute a change in strength for which a suitability petition is required under 21 CFR 314.93(c).

C. Patent Certification and Exclusivity Statement

1. Patent Certification

Except as provided in 21 CFR 314.94(a)(12)(iv), the applicant must provide a certification with respect to each patent issued by the United States Patent and Trademark Office that in the opinion of the applicant and to the best of its knowledge claims the RLD or claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the act [21 U.S.C. 355(j)] and for which information is required to be filed under section 505(b) of the Act (21 U.S.C. 355(b)) and 21 CFR 314.53. As stated under this section of the Act and 21 CFR 314.94(a)(12), the applicant must provide for each patent the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

- That the patent information has not been submitted to the FDA. The applicant shall title such a certification "Paragraph I Certification."

- That the patent has expired. The applicant shall title such a certification "Paragraph II Certification."

- The date on which the patent will expire. (e.g. Patent No. _____will expire on _____.) The applicant shall title such a certification "Paragraph III Certification."

- Or, that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the drug product for which the abbreviated application is submitted. (This type of certification indicates that the applicant is challenging the patent). The applicant shall

title such a certification "Paragraph IV Certification."

A Paragraph IV certification must be accompanied by a statement that the applicant will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under 21 CFR 314.95 with respect to the content of the notice.

Under 21 CFR 314.94(a)(12)(i)(A)(1), applications for Fludeoxyglucose F 18 Injection must contain a Paragraph I certification if patent information has not been submitted to the Agency.

Example of a Paragraph I patent certification follows:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug, 21 CFR 314.94(a)(12)(ii).

A list containing patent information may be located in the Patent and Exclusivity Addendum in the Orange Book and its supplements. Patent information should be verified with the latest Orange Book edition and/or supplement.

2. Exclusivity Statement

Exclusivity is granted by the Agency for certain drug products (21 CFR 314.108). A list containing exclusivity information can be located in the Patent and Exclusivity Addendum in the Orange Book and its supplements. (See also letters dated Oct. 31, 1986, April 28, 1988, and July 29, 1988.)

A statement addressing exclusivity must be submitted even if no exclusivity exists [314.94(a)(3)(ii)].

Example where no exclusivity exists (pertaining to Fludeoxyglucose F18 Injection): According to the publication, Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) *the reference listed drug is not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the act [21 U.S.C. 355(j)(4)(D)]*.

Exclusivity information should be verified with the latest *Orange Book* edition

and/or supplement.

D. Comparison Between Generic Drug and Reference Listed Drug

1. Conditions of Use

Under CFR 314.94(a)(4), the applicant must submit a statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the RLD. The applicant is required to reference the annotated proposed labeling and the currently approved labeling for the RLD [21 CFR 314.94(a)(4)].

2. Active Ingredients

The applicant must provide a statement that the active ingredient in the proposed drug product is the same as the active ingredient in the RLD (21 CFR 314.94(a)(5)(A)). The applicant must also reference the annotated proposed labeling and the currently approved labeling for the RLD (21 CFR 314.94(a)(5)(B)).

3. Route of Administration, Dosage Form, and Strength

Under 21 CFR 314.94(a)(6), the applicant must provide a statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the RLD except for any differences that have been the subject of an approved ANDA suitability petition. The applicant should reference the annotated proposed labeling and the currently approved labeling for the RLD. If differences exist due to the approval of an ANDA suitability petition, these differences should be delineated and a copy of the approval letter for the petition should be included.

Example format follows:

The conditions of use prescribed, recommended, or suggested in the labeling proposed for the generic drug have been previously approved for the reference listed drug. [Please refer to the labeling section for a comparison of (applicant's) annotated proposed labeling and to the currently approved labeling for the reference listed drug.] The active ingredient, route of administration, dosage form, and strength are the same as the reference listed drug.

A detailed comparison of the proposed drug and the reference listed drug follows:

	Generic Drug Product	*Downstate Clinical PET Center*
Conditions of use:	*FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*	*FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*
Active ingredient:	*Fludeoxyglucose F 18*	*Fludeoxyglucose F 18*
Route of administration:	*Parenteral*	*Parenteral*
Dosage form:	*Solution*	*Solution*
Strength:	*6.8 - 35.7 mCi/mL*	*6.8 - 35.7 mCi/mL*

Under 21 CFR 314.93, a change from the RLD in strength, dosage form, or route of administration requires the submission of a suitability petition to obtain permission to file an ANDA with such a change. According to the Orange Book, the strength of the RLD for Fludeoxyglucose F18 ([^{18}F]FDG) Injection is 6.8 - 35.7 mCi/mL. The labeling of the drug product states that it contains 296 ± 3 mL of isotonic saline. Any change that affects the amount of the active ingredient or the concentration of the drug product (in mCi/mL) will be deemed to be a change in strength that, under 21 CFR 314.93, requires a suitability petition prior to filing the ANDA. Therefore, the use of a higher energy cyclotron may result in a more concentrated drug product for which a suitability petition is required under 21 CFR 314.93. In addition, a change in the total volume, and/or the amount of active ingredient, may result in a change of strength for which 21 CFR 314.93 requires a suitability petition.

E. Labeling

Refer to the *Fludeoxyglucose F18 Injection Labeling Guidance* and the Aug. 4, 1993, letter.

A side-by-side comparison of the container labels and package insert with all differences annotated and explained for the RLD and the proposed drug product must be submitted in addition to the four copies of draft (or 12 copies of final printed)

labeling (21 CFR 314.94(a)(8)).

F. Bioavailability and Bioequivalence

The applicant is required to provide information that shows that the drug product is bioequivalent to the RLD product upon which the applicant relies (21 CFR 314.94(a)(7)). (See also 21 CFR 314.94(a)(9)(ii) and (iii) and 21 CFR 320.22(b)(1).)

Any qualitative or quantitative differences in formulation from the RLD for parenteral drug products should be characterized and explained. A side-by-side comparison of the formulation of the proposed product and the RLD should be submitted. Analytical information and a physicochemical comparison should be included. Parenteral drug products may only differ in preservative, buffer, or anti-oxidant. If other changes are made in a parenteral drug product, an in vivo bioequivalence study may be needed.

Inactive ingredients used in the proposed generic drug product should have been previously approved in another drug product given by the same route of administration. The use of an approved inactive ingredient can be verified in the *Inactive Ingredient Guide*. The quantities of the inactive ingredient should not exceed the *Inactive Ingredient Guide* range. (Also refer to the *Interim Inactive Ingredients Policy* for information regarding exception and nonexception excipients.)

A waiver of evidence of in vivo bioequivalence may be requested for Fludeoxyglucose F 18 Injection. For certain drug products, such as Fludeoxyglucose F18 injection (abbreviated as [^{18}F]FDG), the in vivo bioequivalence may be self-evident. The FDA will waive the requirement for the submission of evidence obtained in vivo demonstrating bioequivalence if FDA determines that in vivo bioequivalence is self-evident. For example, in vivo bioequivalence may be self-evident if the drug product meets the following criteria:

- The drug product is a parenteral solution intended solely for administration by injection.

- The drug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application [21 CFR 320.22(b)].

Example of request for waiver of evidence of in vivo bioequivalence:

The (applicant) requests that the FDA waive the requirement for the submission of evidence demonstrating in vivo bioequivalence for (the proposed drug product). The

(drug product) meets the provisions of 21 CFR 320.22(b)(1)(i) and (ii).

In addition, under 21 CFR 320.22(e), for good cause, FDA may waive a requirement for submission of evidence of in vivo bioavailability if FDA determines that a waiver is compatible with the protection of the public health.

G. Components and Composition

Components (active and inactive ingredients) and composition of the drug product should be included. For Fludeoxyglucose F18 Injection, the active ingredient (drug substance) is Fludeoxyglucose F 18 (2-deoxy-2-[^{18}F]fluoro-D-glucose).

All inactive ingredients should be identified by their chemical names and their quantity and/or concentration (e.g., mg/mL) should be included. Applicants should refer to 21 CFR 314.94(a)(9)(iii) concerning the inactive ingredient changes permitted in a generic drug product intended for parenteral use. If inactive ingredients in the proposed product differ qualitatively and/or quantitatively from the RLD, information should be provided to demonstrate that the difference does not affect the safety of the proposed drug product. The submitted information should include, but need not be limited to, the following: (1) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and are within the same concentration range, (2) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (3) a comparison of the physical and chemical properties (e.g., pH, osmolarity, toxicity) of the proposed drug product with that of the RLD, and (4) information to show that the inactive ingredients do not affect these properties.

For [^{18}F]FDG, the Agency recognizes that the drug product formulated at the end of the synthesis (i.e., a batch) may be used as a single dose or as multiple doses. The quantitative composition of the unit dose may be assumed to be the same as that of the entire batch.

H. Raw Materials Controls

Information concerning the raw materials used for the manufacture of [^{18}F]FDG may be provided in the following format:

1. Components

    a. Name and Full Address(es) of the Supplier.

b. Method of Purification

If a component (e.g., mannose triflate, kryptofix) as received from its supplier is further purified or recrystallized, full information on this process, including the rationale, the method(s), and the solvents employed (if any) should be included in the application.

c. Specifications and Analytical Test Methods

For each component and inactive ingredient, the following information should be included:

i. The applicant should provide specifications and a test method for the identity of all components. The identity test should be performed prior to release of each lot of the material. Details of the analytical test method should be included in the application.

ii. If the suppliers of the raw materials are different than those listed in the RLD, then the suppliers should be validated. All raw material components should have acceptance specifications and be accepted with a certificate of analysis (COA). Full testing to determine the accuracy of the COA should be preformed. The supplier of the raw materials should be in compliance with Current Good Manufacturing Practice (CGMP) regulations. Once a supplier is validated, and a manufacturer wants to change suppliers, then the application should include data which demonstrates that the [^{18}F]FDG produced from raw materials from a new supplier are equivalent to the current supplier in terms of conformance with established specifications.

d. Retest Schedule

Each raw material should be retested periodically to determine that it still meets specifications. The periodic retest schedule should be provided.

2. Inactive Ingredients

For each inactive ingredient used in the drug product formulation, a statement

of its quality [e.g., American Chemical Society (ACS), United States Pharmacopeia (USP), National Formulary (NF)] should be provided. A certificate of analysis from a validated supplier that includes specifications and test results may be used to accept this material.

3. All Other Components (e.g. reagents, solvents)

A list of all other components which are used in the synthesis and purification of the drug product (e.g., all reactants, chemicals, solvents, reagents, that were not included above) should be included. A statement of the quality [e.g., American Chemical Society (ACS), United States Pharmacopeia (USP), National Formulary (NF)] of each component should be provided. A certificate of analysis, from a validated supplier, that includes specifications and test results may be used to accept this material.

4. Reference Standard

For [^{18}F] FDG, 2-deoxy-2-fluoro-D-glucose, a nonradioactive reference standard is used to establish and/or to verify the identity of Fludeoxyglucose F18 in the drug product. It also may be used for the determination of specific activity. The following information should be provided:

a. Source

Name and address of the supplier. If the reference standard is synthesized in-house, a statement to this effect should be included.

b. Proof of Identity

If the reference standard is purchased commercially, the applicant should include the certificate of analysis from its supplier. If the material is synthesized in-house, representative data to establish unequivocally the identity of the reference material lot as 2-deoxy-2-fluoro-D-glucose should be provided. The documentation should include complete spectrophotometric data, other applicable analytical data, as well as information on the synthetic route used.

I. Description of Manufacturing Facility

The following information should be provided (see also 21 CFR parts 210 and 211):

1. Name and full address(es) of the facility(ies) [including building and room numbers] used in manufacturing, packaging, release testing, and stability testing of the drug product. Please include the Registration Number of the facility.

2. Certification that the facility is in compliance with the Current Good Manufacturing Practices (CGMPs) (see also letter of Oct. 14, 1994, on field/headquarters agreement). The applicant and any contract facilities should provide the following statement with an original signature.

(Name of Applicant) certifies that the methods used in and the facilities and controls used for the manufacturing, processing, packaging, testing, and holding of (product) conform, and will continue to conform, to the Current Good Manufacturing Practice regulations under 21 CFR parts 210 and 211.

J. Outside Firms Including Contract Testing Laboratories

The following information should be provided:

1. Name and full address of each facility. Please include the Registration Number.

2. The function(s) of each facility.

3. A certification that the facility is in compliance with the CGMPs.

K. Manufacturing and Processing Instructions

1. Manufacture of Drug Substance

The following information should be submitted:

a. Batch Formula

The batch formula for the test batch(es) (e.g., the batch used in support of the application) and the proposed production batches should be included. A complete list of all the ingredients (whether or not they remain in the finished product) and their amounts used in the batch formulation should be provided.

b. Production of the Radionuclide

i. Description of the Particle Accelerator

A brief description of the particle accelerator including its make and model should be provided. Applicants should note that the validation information on the accelerator demonstrating that the equipment is capable of consistently operating within the established limits and tolerances should be available on site for inspection.

ii. Operating Parameters

Operating parameters for the production at the manufacturing site should be defined. Examples of the operating parameters that should be included are maximum particle energy, beam current, and irradiation (bombardment) times. The value(s) or range of values for each defined operating parameter should be included in the application.

iii. Target Body

Specifications for the target body and the foil(s) which come in contact with the target material should be provided. These should include the composition of the target body and foil materials and the volume of the target. Information should be provided on procedures which are used to establish equivalency when an existing target body and/or foil(s) are replaced.

iv. Recycling of Oxygen-18 Enriched Water

If oxygen-18 [^{18}O]water is not recycled, this fact should be so stated. If it is recycled, procedures used for its reprocessing should be described. Information should be provided to demonstrate that the recycling and/or reprocessing of [^{18}O]water does not change the drug product quality impurity profile.

c. Synthesis and Purification of Drug Substance

i. Description of Radiochemical Synthesis and Purification Equipment

The equipment used for the synthesis and purification of

Fludeoxyglucose F18 should be described. It should include a schematic flow diagram of the equipment from the target to the vial filling unit. A description of various components (e.g., tubing, reaction vessel, columns, and the function of each purification component (e.g., various columns) should be included. The components that are replaced after each manufacturing operation, and the components that are replaced periodically should be identified. Suppliers for each of the replaceable components (e.g., various purification columns and filter) should be provided. The procedures used in the assembly of components should be described.

ii. Description of Radiochemical Synthesis and Purification Operation

Identify the components and the processes that are under computer control and the ones that are under manual control. Applicants should note that the validation information demonstrating that the equipment is capable of consistently operating within the established limits and tolerances should be available on site for inspection.

A stepwise description of the radiochemical synthesis and purification operation, including in-process controls (refer to section L.), should be provided. An acceptable range of yields of the radioactivity for the drug product should also be provided. The proposed range of yields should be justified.

iii. Post Synthesis Operations

A description of how the synthesis and purification equipment is prepared for a subsequent batch should be provided. All cleaning and purging procedures should be fully described.

2. Manufacture of Drug Product

a. Production Operations

The procedures used in the manufacture of the drug product should be described.

b. Reprocessing of the Drug Product

A drug product batch should not be reprocessed unless the reprocessing procedures and conditions have been approved in the ANDA. If an applicant intends to reprocess a drug product batch, the conditions (circumstances) and full reprocessing procedures should be submitted.

c. Proposed Master Production Records [21 CFR 314.94(a)(9)(i)]:

A copy of the blank master production record, including a description of the equipment, to be used for the manufacture of a lot of the drug product should be included.

3. Microbiological Validation

a. Introduction

i. Purpose

The recommendations in this document apply to ANDAs for sterile [^{18}F]FDG. These recommendations also apply to approved applications when supplements associated with sterile processing are submitted.

ii. Documenting Sterilization Process Validation

Sterilization process validation data should be generated using procedures and conditions that are fully representative and descriptive of the procedures and conditions proposed for manufacture of the product in the application.

The Center recognizes that for most [^{18}F]FDG products, the final drug product will be manufactured using aseptic techniques rather than terminal sterilization. The Center also recognizes that conventional methods for the validation of aseptic processes may not apply to the validation of the sterile production of [^{18}F]FDG due to the very small number of product units manufactured from a batch or lot, and its short half-life.

Technical subsections of an application are often reviewed apart from the main body of the application. For this reason, it is

recommended that the microbiology subsection include an introductory description of the drug product (syringe, vial, glass, plastic, closure system) and the product's intended use. It is further recommended that the information describing sterilization processes be filed in a subsection (or volume) of the chemistry manufacturing, and controls (CMC) portion of an application. This permits the CMC subsections to be reviewed simultaneously by different reviewers in different locations.

b. Information for Terminal Moist Heat Sterilization Processes

It is not expected that FDG-F18 products will be sterilized by terminal moist heat processes. Information relating to aseptic processing for the manufacture of FDG-F18 drug products is provided under "Information for Aseptic Fill Manufacturing Processes" (section c.). However, should FDG-F18 be sterilized by terminal moist heat methods, information should be submitted in support of sterility assurance as described in Section II of the *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

c. Information for Aseptic Fill Manufacturing Processes

The following types of information should be submitted in support of sterility assurance for FDG-F18 manufactured by aseptic processing. The finished drug product should be described including the product solution (i.e., composition and pH) and the container-closure system(s) to be sterilized including size(s), fill volume, or secondary packaging. The route of product administration and the range of product dosage should be provided.

i. Buildings and Facilities

A brief description of the manufacturing building and aseptic facilities should be provided. The following information should be included.

- Floor Plan - A floor plan of the area(s) housing the aseptic filling facilities including preparation areas should be provided. The air cleanliness class of each area should be identified (e.g., Class 100, Class 10,000, Class

100,000). Isolators or barrier systems should be identified.

- Location of equipment - The placement of all critical equipment including, but not limited to, laminar flow hoods, autoclaves, and filling devices should be identified. Equipment within barrier or isolation systems should be noted.

ii. Overall Manufacturing Operation

The overall manufacturing operation including, for example, solution compounding, component preparation, filling, capping, and aseptic assembly should be described. The normal flow (movement) of product and components from formulation to finished dosage form should be identified and indicated on (or in relation to) the floor plan described above. The following information should be considered when describing the overall manufacturing operation.

- Drug Product Solution Filtration - The specific bulk drug product solution filtration processes, including the use of tandem filter units, prefilters, and bacterial retentive filters should be described. A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product. For simple aqueous solutions, a certification from the filter manufacturer is often adequate. Effects of the filter on the product formulation should be described (e.g., adsorption of preservatives or active drug substance, or extractables).

- Specifications Concerning Holding Periods - 21 CFR 211.111 requires the establishment of appropriate time limits for completing each phase of production to ensure the quality of the drug product. Therefore, specifications concerning any holding periods between the compounding of the bulk drug product and its filling into final containers should be provided. These specifications should include, for example, times, temperatures,

conditions of storage. Procedures used to protect microbiological quality of the bulk drug or components during these holding periods should be indicated. Maintenance of the microbiological quality during holding periods may need verification. These technical burdens may be reduced if components of the drug solution are prepared fresh each day and maintained sterile prior to compounding.

- Critical Operations - The critical operations that expose product or product contact surfaces to the environment (such as transfer of sterilized containers or closures to the aseptic filling areas) should be described. Any barrier or isolation systems should be described.

iii. Sterilization and Depyrogenation of Containers, Closures, Equipment, and Components

The sterilization and depyrogenation processes used for containers, closures, equipment, components, and barrier systems should be described. A description of the methods for validation of these processes should be provided including, where applicable, heat distribution, and penetration summaries, biological challenge studies (microbiological indicators and endotoxin), and routine monitoring procedures. Data (including controls) demonstrating distribution and penetration of the sterilant and microbiological efficacy of each process should be submitted. For applicants using drug product containers which are purchased sterile from a vendor, a certificate from the vendor may be provided to substitute for the above information.

- Bulk Drug Solution Components That are Sterilized Separately - If the bulk drug solution is aseptically formulated from components that are sterilized separately, information and data concerning the validation of each of these separate sterilization processes should be provided.

- Sterilization Information in the Batch Records - The batch record supplied with the chemistry, manufacturing, and controls section of the application should identify the validated process(es) to be used for sterilization or

depyrogenation of any container-closure components. This information may be included in the batch record by reference to the validation protocol or standard operating procedure (SOP), or by reference to the vendor certificate for drug product containers purchased sterile from a vendor.

iv. Procedures and Specifications for Media Fills

Media fills are simulated manufacturing operations using microbiological growth medium in place of drug product. The procedures and specifications used for media fills, and summaries of results for validation using the same container-closure system and filling process that is to be used for the product should be described. The microbiological testing method(s) used should be described. Any procedural deviations between the media fill and the production process should be indicated. A summary of recent media fill results (usually for at least 3 successful trials), including failures, should be provided.

v. Actions Concerning Product When Media Fills Fail

Descriptions of investigation plans and appropriate corrective actions should be provided.

vi. Microbiological Monitoring of the Environment

The microbiological monitoring program used during routine production and media fills should be described. The frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded should be included.

- Exceeded Limits - A description of the actions taken when environmental microbiological specifications are exceeded should be provided.

vii. Container-Closure and Package Integrity

The methods and results demonstrating the integrity of the microbiological barrier of the container-closure system should be

summarized. This should include testing for initial validation. For initial validation of microbiological integrity of container-closure systems, product sterility testing is not normally considered sufficient.

viii. Test Methods and Release Criteria

Product release tests for injectable products include sterility and pyrogenicity (or endotoxins) assessments as prescribed in 21 CFR 211.167(a). However, 21 CFR 211.165(a) permits the release of batches of drug composed of short-lived radiopharmaceuticals prior to the completion of sterility and pyrogen testing, but requires that such testing of each batch be started "as soon as possible." The laboratories performing these tests (particularly contract laboratories) should be identified and these should be in compliance with CGMP requirements.

- Sterility Test - Sterility test methods for [^{18}F]FDG will usually differ significantly from compendial test methods, so a clear description of the test should be provided. Procedures should be described and include the protocol for the selection of samples for testing. Testing performed within barrier systems should be discussed, and information concerning validation of the barrier system may be necessary.

- Bacterial Endotoxins Test and Method - Describe the bacterial endotoxins test for the product. This description should include qualification of the laboratory, inhibition, and enhancement testing and results, determination of noninhibitory concentration and maximum valid dilution. For further information see the agency guidance entitled *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*.

ix. Evidence of Formal Written Procedures

Evidence should be provided that there are formal, written procedures describing the above elements. Such evidence may

consist of standard operating procedures (SOPs), or a listing of SOPs or protocols submitted as part of the elements listed above.

d. Maintenance of Microbiological Control and Quality: Stability Considerations

Due to the extremely short period of use for FDG-F18, stability considerations with regard to microbiological quality are greatly abbreviated.

L. In-Process Controls

1. In-Process Controls

A description of any in-process controls should be provided. Examples of procedures that may be performed are the yields of fluoride ions (in mCi), temperature of the reaction vessel, gas pressure and/or flow rate, and synthesis time. In certain automated units, it may not be possible to directly monitor certain in-process parameters. In this case, it should be so stated.

2. Copy of Executed Batch Record

An executed batch record for a representative batch should be submitted. The following information should be included in accordance with 21 CFR 314.50(d)(1)(ii)(b):

- The specifications and test procedures for each component and for the drug product;
- Names and addresses of all facilities involved in manufacturing, processing, packaging, and testing of the drug product and identification of the operation performed by each facility;
- The name and address of the supplier of the container/closure system;
- The results (primary data) of any tests performed on the components of the drug product, as required by 21 CFR 211.165.

Applicants should note that although records for other batches (validation and/or stability) used to support the application, need not be included in the submission, additional information on these may be requested during the review process. Batch records for all the batches used to support the application should be available on site for inspection.

M. Labeling Procedures

The procedure for labeling of the drug product should be described.

N. Container

The following information regarding the container/closure should be provided:

- Name and full address of the manufacturer of the container/closure system or individual components. Appropriate DMF reference(s), if any, and the letter(s) of authorization (LOA) should be included in the ANDA;
- Container glass type (refer to USP chapter < 661 >); Composition of the stopper and crimp seal (e.g., aluminum);
- Physical description (e.g., size, shape, volume, product catalog number);
- Container/closure compatibility, including leaching
- Acceptance specifications and tests performed.

O. Controls for the Finished Dosage Form

For general information on controls for the drug product, refer to the *Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products*

1. Sampling Procedures

If multiple vials are manufactured, a sampling plan should be provided to assure that the test sample of the drug product is representative of the entire batch. However, if only one vial is manufactured, the description of the sampling procedure should be limited to the amount (volume) that is withdrawn from the final container and how it is distributed among the individual tests.

2. Regulatory Specifications, Methods, and Testing Schedules

The application should provide a list of specifications and identify the test methods (by name and code number) used to control the identity, strength, quality, and purity of the drug product. A schedule for performing each proposed test (i.e., pre or post release, frequency of testing) should be included. For [^{18}F]FDG, applicants should refer to section P "Analytical Methods" below for a list of tests that may satisfy the relevant identity, strength, quality, and purity criteria.

P. Analytical Methods

In this section, full details of the analytical test methods should be provided. The following is a list of tests and schedules which, in the current opinion of the Agency, satisfy the identity, strength, quality, and purity criteria for the drug product.

1. Appearance

The test method and specifications for the appearance of the drug product should provide insurance that the drug product is clear, colorless, and free of particulate matter. This may be accomplished by visualization of the drug product through leaded glass. If, due to radiation safety considerations, the ability to visually inspect [^{18}F]FDG is limited, one acceptable approach is to incorporate procedures to provide that: (1) each component or container-closure system is inspected individually for visual evidence of particulate, foreign matter, and container-closure defects immediately before use; (2) defective components will not be used; and (3) the batch production and control record of the [^{18}F]FDG includes a signed or initialed verification that such inspection was conducted and that only acceptable finished articles were used.

2. Identity Tests(s)

Test methods and specifications for the radionuclidic and radiochemical identity of the drug product should be described.

a. Radionuclidic

The radionuclidic identity should be established on every batch of the drug product by the method described in the USP monograph for Fludeoxyglucose F18 Injection.

b. Radiochemical

The radiochemical identity may be established by a chromatographic procedure by comparing the radioactive drug product with the well characterized nonradioactive 2-deoxy-2-fluoro-D-glucose reference standard in a procedure such as HPLC or TLC. The radiochemical identity test should be performed on every batch of the drug product prior to its release.

3. Assay (Radioconcentration)

Specifications (range), in mCi/mL, and the method of determination of radioconcentration of the drug product should be described. The method should clearly describe the procedure used for the determination of total radioactivity and the procedure used for the determination of the final volume in the container. This test should be performed on every batch of the drug product prior to its release.

4. Specific Activity

For [^{18}F]FDG, if a no-carrier added synthetic route is used, the specific activity need not be determined on a routine basis provided it is validated. Validation requires that the applicant of provide a drug product with consistent specific activity that at least meets the USP monograph requirements.

5. Purity

a. Radiochemical Purity

Specification and test method(s) for the radiochemical purity of the drug product should be described. A test method based on USP Fludeoxyglucose F18 Injection monograph may be acceptable. The radiochemical purity test method should be specific for Fludeoxyglucose F18. Applicants should demonstrate that the radioactivity associated with potential radiochemical impurities does not interfere with the measurement of radioactivity peak associated with Fludeoxyglucose F18. The radiochemical purity test should be performed on every batch of the drug product prior to its release.

b. Stereoisomeric Purity

In synthetic methods, where there is a possibility of formation of a stereoisomeric impurity (e.g., contamination of α and β anomers of fluorodeoxymannose in the electrophilic substitution synthesis method), a specification and a test method for the stereoisomeric purity should be provided. The drug product should meet the USP Fludeoxyglucose F18 Injection monograph for stereoisomeric purity requirements.

c. Radionuclidic Purity

Specifications for the radionuclidic purity and method for its determination should be described. The test method described in the

USP monograph may be used. With acceptable validation, the radionuclidic purity test may be performed after release of the drug product on the day of manufacture.

d. Chemical Purity

This drug product may be manufactured using different synthetic routes and processes and, therefore, may contain different impurities. Specifications, suitable methods, and schedules of testing for each impurity should be provided in the application. For example, if an applicant uses the Fludeoxyglucose F18 synthesis described by Hamacher et.al. [J. Nucl. Med. 27, 235-238 (1986)], then the residual amounts of kryptofix and the organic solvents employed in its manufacture may need to be monitored prior to the release of every batch of the drug product. Levels of other chemical impurities that may be found in the drug product (e.g., 2-chloro-2-deoxy-D-glucose) should be determined.

6. Pharmaceutical Quality

a. pH

A specification and the method of determination of pH of the drug product should be provided. The pH test should be performed prior to the release of every batch of the drug product. A pH paper test method may be acceptable, if performed using the reference standards at the lower and the upper range (with some allowance for the inaccuracy of the method) of the specifications. Applicants should note that during the shelf life, the pH of the drug product must remain within the proposed limits.

b. Osmolarity

Applicants should provide information that [^{18}F]FDG will yield a reproducible osmolarity.

c. Membrane Filter Integrity Test

The integrity of the membrane filter used to sterilize the radiochemical product should be assessed prior to the release of the drug product. The test method and specifications should be provided in the application.

The bubble point measurement method may be used to test the membrane filter integrity.

d. Bacterial Endotoxin Testing

The test should be performed on every batch.

e. Sterility Testing

The test should be performed on every batch.

7. Method Validation

The applicant should only submit those methods in the method validation package that are non USP methods.

Q. Stability of Finished Dosage Form[3]

1. Selection and Number of Batches

Where a 60 minute irradiation time is employed, a single stability batch will suffice. Where a range of irradiation times are employed, three additional batches of the drug product manufactured at the upper end should be studied.

2. Proposed Expiration Dating Period

An expiration dating period for the drug product, based on its stability, should be proposed in the application. The drug product should meet all specifications at expiry.

3. Test Procedures

Full testing should be performed at the initial time point (i.e., at release) and at the expiry period. Because of the short expiration dating period, the sterility and bacterial endotoxin testing need only be performed at release.

4. Storage Conditions

[3] The ICH Q1A guideline, *Stability Testing of New Drug Substances and Products*, and the *Guideline for Submitting Documentation For the Stability of Human Drugs and Biologics*(Stability Guidance) provide broad guidance in designing the stability studies for drug products.

Stability studies should be performed in the same container/closure system and at the same temperature in which the drug product will be stored during its shelf life (e.g., the drug product vial). The vial should be stored in the inverted position during the stability study.

5. Analytical Results on Stability Batch

The stability study analytical results should be provided in the application. Relevant information should include batch number, date of manufacture, storage condition, vial position, total radioactivity, and radioconcentration.

6. Postapproval Stability Protocol

The first three production batches are to be placed on the stability protocol. After the marketing approval of an ANDA, one production batch per year should be placed on the stability protocol.

R. Samples

If the analytical methods are to be validated in FDA laboratories, the applicant will be notified when samples should be provided. See also 21 CFR 314.94(a)(10) and 21 CFR 314.50(e)(1) and (e)(2)(i).

S. Other Information

Copies of cited references, their English translation (if not in English), and letters of authorization must be included as part of the other information in the application (21 CFR 314.50(g)(1) and (2)).

IV. REFERENCES[4]

Letters to Industry

October 31, 1986, letter to all NDA and ANDA holders and applicants on patent issues and the three-year exclusivity provisions.

[4]The reference documents are available from the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; (tel) 301-827-4573.

April 28, 1988, letter from the Director, Center for Drug Evaluation and Research, to all NDA and ANDA holders and applicants on the Drug Price Competition and Patent Term Restoration Act of 1984. The letter focuses on the three- and five-year exclusivity provisions.

July 29, 1988, letter from the Director, Center for Drug Evaluation and Research, to industry on the Drug Price Competition and Patent Term Restoration Act of 1984.

November 8, 1991, letter from the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to industry on improving the efficiency and effectiveness of the generic drug review process.

July 27, 1992, letter from the Deputy Commissioner for Operations to drug manufacturers/industry associations on the 1992 Generic Drug Enforcement Act, specifically on debarment certification and convictions statements.

January 15, 1993, letter from the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to all ANDA and AADA applicants regarding refusal to file and refusal to approve incomplete applications based on the new requirements of the 1992 Generic Drug Enforcement Act.

August 4, 1993, letter from the Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to industry providing information on labeling, scale-up, packaging, minor/major amendment criteria, and bioequivalence requirements.

April 8, 1994, letter from the Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to all ANDA and AADA applicants on a variety of application-related issues. This letter also contains a list of industry questions and Agency answers resulting from the August 4, 1993, letter to industry.

October 14, 1994, letter from the Director, Center for Drug Evaluation and Research and the Associate Commissioner for Regulatory Affairs to all NDA, ANDA, and AADA applicants on the roles of CDER chemistry review scientists and Office of Regulatory Affairs field investigators.

Guidance Documents

International Conference on Harmonisation. 1994. *Stability Testing of New Drug Substances and Products*, ICH-Q1A, September 1994.

U.S. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) and Center for Veterinary Medicine (CVM). 1994. *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, November 1994.

DHHS, FDA. 1987. *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*, February 1987.

DHHS, FDA. 1987. *Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products*, February 1987.

DHHS, FDA, CDER. *Approved Drug Products With Therapeutic Equivalence Evaluations*.

DHHS, FDA, CDER, Office of Compliance. 1987. *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices,* November 1987.

DHHS, FDA, CDER, Office of Generic Drugs. 1997. *Fludeoxyglucose F18 Injection Labeling Guidance*, January 1997.

DHHS, FDA, CDER, Office of Generic Drugs. 1994. *Interim Inactive Ingredients Policy*, November 17, 1994.

DHHS, FDA, CDER, Office of Management. *Inactive Ingredient Guide*.

DHHS, FDA, CDER. 1997. *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*, April 1997.

Guidance for Industry

Content and Format of an Abbreviated New Drug Application (ANDA) — Positron Emission Tomography (PET) Drug Products

With specific information for ANDAs for Fludeoxyglucose F18 Injection

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Draft release for comment on: April 18, 1997.

Comments and suggestions regarding this draft document should be submitted by June 28, 1997, to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm 1-23, Rockville, MD 20857. All comments should be identified with the docket number 97D-0164. For questions regarding this draft document, contact Peter Rickman, at (301) 594-0315.

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

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Draft — Not for implementation

GUIDANCE FOR INDUSTRY[1]

CONTENT AND FORMAT OF AN ABBREVIATED NEW DRUG APPLICATION (ANDA) — POSITRON EMISSION TOMOGRAPHY (PET) DRUG PRODUCTS

With specific information for ANDAs for Fludeoxyglucose F18 Injection

I. INTRODUCTION

Under 21 U.S.C. 355(j), Abbreviated New Drug Applications (ANDAs) may be submitted for drug products that are the same as a listed drug. FDA's implementing regulations at 21 CFR 314.92 state that the term *same as* means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except for those uses for which approval cannot be granted because of exclusivity, or for which an existing patent may be omitted. Because a New Drug Application (NDA) for Fludeoxyglucose F18 Injection was submitted by Downstate Clinical PET Center and was approved on August 19, 1994, (NDA 20-306), ANDAs may be submitted for drug products that are the same as this reference listed drug (RLD) product.

This guidance is provided to assist applicants who wish to submit an ANDA for Fludeoxyglucose F18 Injection. The Center for Drug Evaluation and Research's *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*, provides information regarding the organization of an ANDA.

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[1]This draft guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This draft guidance represents the Agency's current thinking on the content and format of an ANDA for PET radiopharmaceutical drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, CDER, FDA, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, (Internet) http://www.fda.gov.cder/guidance.htm.

II. GENERAL INFORMATION

The content and format of abbreviated applications is described in 21 CFR 314.94. This regulation also requires the submission of three copies of the application: an archival copy, a review copy, and a field copy.[2]

An applicant should submit a complete archival (original) and review (duplicate) copy of the application that includes the following information:

A. Cover Letter

The application should include a signed and dated cover letter which includes a clear, brief introductory statement. The cover letter should be on the letterhead stationery of the applicant. The cover letter should contain the following information:

1. Purpose of the submission;

2. Type of submission (ANDA, AADA, amendment, supplement, annual report, or resubmission as a result of prior withdrawal of an application);

3. Name, title, signature, and address of the applicant;

4. Proprietary name (if any) and established name of the drug product;

5. Number of volumes submitted.

B. Letters of Authorization

1. Agent

Domestic Applicants - If a domestic firm uses an agent, a letter of authorization allowing the agent to act on behalf of the applicant should be included in the application following the cover letter.

2. Drug Master File (DMF)

[2] On March 20, 1997, FDA published a final rule (62 FR 13429) that would allow FDA to accept, under certain circumstances, electronic records and electronic signatures as equivalent to paper records and handwritten signatures executed to paper. This rule takes effect on August 20, 1997. For information on how to prepare an electronic ANDA contact the Office of Generic Drugs.

DMF letters of authorization grant the Agency the authority to refer to information in a DMF during the review of an ANDA (21 CFR 314.420). The letter of authorization should be on the DMF holder's letterhead, and dated and signed with an original signature. The letter should cite the DMF holder's name, drug name, and DMF number. If the referral is made by a third party (i.e., another corporate entity, agent, or supplier), a letter from the DMF holder should be provided giving the third party the authorization to grant referrals to the DMF. If the applicant intends to rely on DMF information concerning the bulk drug substance, authorization should be granted by the holder of the DMF for each source of bulk drug substance. This letter should be placed in the chemistry, manufacturing, and controls section along with the information submitted for the active ingredient. (See also letters dated Nov. 8, 1991, and April 8, 1994.)

If the applicant is also the manufacturer of the active ingredient, Fludeoxyglucose F18 applicants would not have to provide a DMF reference for the bulk drug substance.

C. Debarment Certification/List of Convictions

Use of a debarred individual/firm, within the meaning of 306(a) and (b) of the Federal Food, Drug and Cosmetic Act (the act) [21 U.S.C. 335a(a) and (b)], may preclude the approval of the application.

The 1992 Generic Drug Enforcement Act authorizes the FDA to debar an individual, convicted of certain crimes or found to have engaged in certain types of conduct, from providing any services to a drug product applicant. The law also authorizes the FDA to debar a firm convicted of certain crimes from obtaining or participating in certain subsequent drug approvals.

Under section 306(k)(2) of the act [21 U.S.C. 335a(k)(1)], any application for approval of a drug product submitted after June 1, 1992, must include a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)] in connection with such application. In addition to the certification requirement, section 306(k)(2) of the act [21 U.S.C. 335a(k)(2)] requires that all ANDAs and AADAs contain a conviction information statement listing any convictions the firm or its affiliated persons may have that could lead to debarment. The applicant should provide a list of any relevant convictions, the name of the person/firm convicted, the title of the section of the federal or state statute involved, the sentencing date, the court entering judgment, and

the case number, if known, and a brief description of the offense. In addition, the applicant should explain the role of each convicted person in the development of the application. The debarment certification and conviction information, which usually follows the cover letter, should be signed by a responsible officer of the applicant or by the individual responsible for signing the application. (See also letters dated July 27, 1992, Jan. 15, 1993, and April 8, 1994.)

Examples of a debarment certification and a conviction information statement follow:

Debarment Certification:

(Name of applicant) certifies that (the applicant) did not and will not use in any capacity the services of any person debarred under section 306 of the act in connection with this application.

If convictions exist for the applicant or an affiliated person responsible for the development or submission of the application that could lead to a debarment, use the following convictions statement.

Convictions Statement:

(Applicant) lists the following convictions for (applicant and/or affiliated persons):

These convictions are described in section 306(a) and (b) of the act [21 U.S.C. 335a(a) and (b)]. The list must contain all such convictions that occurred within 5 years before the date of the application (306(k)(2)).

If neither the firm nor any of its affiliated persons has convictions to list, a statement should be submitted to the effect that neither the applicant nor its affiliated persons responsible for the development or submission of the application has been convicted of a relevant offence within the last five years.

D. Field Copy Certification

The applicant must submit a certification that indicates that an accurate third copy of the technical sections (chemistry, manufacturing, and controls) of the application has been submitted to the appropriate FDA district office (see 21 CFR 314.94(d)(5) and 314.440(a)(4)). This certification should contain an original signature.

If questions arise on issues involving the submission of the third copy, please contact

the Office of Compliance in the Center for Drug Evaluation and Research at (301) 594-0054.

Example of a field copy certification follows:

(Name of applicant) certifies that the field copy is a true copy of the technical section of the application described in 21 CFR 314.94(d)(5).

III. CONTENT AND FORMAT OF AN ABBREVIATED APPLICATION

A. Application Form

Form FDA 356h should be completed, signed with an original signature, and contain the information required under 21 CFR 314.94(a)(1). The form should also list all pertinent DMFs. The applicant should identify the RLD (reference listed drug) on Form FDA 356h.

Under 21 CFR 314.50(a)(3), the applicant must submit a statement as to whether the applicant proposes to market the drug product as a prescription or over-the-counter product. If the correct box is checked on Form FDA 356h regarding prescription or over-the-counter status, no additional statement is necessary.

Each application should include a table of contents [21 CFR 314.94(a)(2)] following Form FDA 356h. For a suggested table of contents, refer to the *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*.

The table of contents helps the reviewer locate information in the application. Each section of the application should be delineated by dividers and tabbed, and the pages should be numbered sequentially.

B. Basis for Abbreviated New Drug Application Submission

The applicant must cite the name of the RLD including its dosage form and strength (21 CFR 314.94(a)(3)(i)), as identified in the publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), by the symbol "+". The product designated with the symbol "+" is the drug product selected by the Agency as the reference standard for conducting bioequivalence testing.

NDA 20-306, Fludeoxyglucose F 18 Injection USP, held by Downstate Clinical PET Center is the applicable RLD.

The ANDA product must have the same active ingredient, dosage form, strength, and route of administration as the reference listed drug product [21 CFR 314.94(a)(5)(i)(A) and 314.94(a)(6)(i)(A)]. A change from the RLD in one or more of these items requires the submission of a suitability petition to obtain permission to submit an ANDA with such change [21 CFR 314.93]. The strength of the drug product refers to the concentration or amount of active ingredient in the drug product. Generally, a change in either the concentration or total volume of a parenteral drug product will constitute a change in strength for which a suitability petition is required under 21 CFR 314.93(c).

C. Patent Certification and Exclusivity Statement

1. Patent Certification

Except as provided in 21 CFR 314.94(a)(12)(iv), the applicant must provide a certification with respect to each patent issued by the United States Patent and Trademark Office that in the opinion of the applicant and to the best of its knowledge claims the RLD or claims a use of such listed drug for which the applicant is seeking approval under section 505(j) of the act [21 U.S.C. 355(j)] and for which information is required to be filed under section 505(b) of the Act (21 U.S.C. 355(b)) and 21 CFR 314.53. As stated under this section of the Act and 21 CFR 314.94(a)(12), the applicant must provide for each patent the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

- That the patent information has not been submitted to the FDA. The applicant shall title such a certification "Paragraph I Certification."

- That the patent has expired. The applicant shall title such a certification "Paragraph II Certification."

- The date on which the patent will expire. (e.g. Patent No. _____will expire on _____.) The applicant shall title such a certification "Paragraph III Certification."

- Or, that the patent is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the drug product for which the abbreviated application is submitted. (This type of certification indicates that the applicant is challenging the patent). The applicant shall

title such a certification "Paragraph IV Certification."

A Paragraph IV certification must be accompanied by a statement that the applicant will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under 21 CFR 314.95 with respect to the content of the notice.

Under 21 CFR 314.94(a)(12)(i)(A)(1), applications for Fludeoxyglucose F 18 Injection must contain a Paragraph I certification if patent information has not been submitted to the Agency.

Example of a Paragraph I patent certification follows:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug, 21 CFR 314.94(a)(12)(ii).

A list containing patent information may be located in the Patent and Exclusivity Addendum in the Orange Book and its supplements. Patent information should be verified with the latest Orange Book edition and/or supplement.

2. Exclusivity Statement

Exclusivity is granted by the Agency for certain drug products (21 CFR 314.108). A list containing exclusivity information can be located in the Patent and Exclusivity Addendum in the Orange Book and its supplements. (See also letters dated Oct. 31, 1986, April 28, 1988, and July 29, 1988.)

A statement addressing exclusivity must be submitted even if no exclusivity exists [314.94(a)(3)(ii)].

Example where no exclusivity exists (pertaining to Fludeoxyglucose F18 Injection): According to the publication, Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) *the reference listed drug is not entitled to a period of marketing exclusivity under Section 505(j)(4)(D) of the act [21 U.S.C. 355(j)(4)(D)]*.

Exclusivity information should be verified with the latest *Orange Book* edition

and/or supplement.

D. Comparison Between Generic Drug and Reference Listed Drug

1. Conditions of Use

Under CFR 314.94(a)(4), the applicant must submit a statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the RLD. The applicant is required to reference the annotated proposed labeling and the currently approved labeling for the RLD [21 CFR 314.94(a)(4)].

2. Active Ingredients

The applicant must provide a statement that the active ingredient in the proposed drug product is the same as the active ingredient in the RLD (21 CFR 314.94(a)(5)(A)). The applicant must also reference the annotated proposed labeling and the currently approved labeling for the RLD (21 CFR 314.94(a)(5)(B)).

3. Route of Administration, Dosage Form, and Strength

Under 21 CFR 314.94(a)(6), the applicant must provide a statement that the route of administration, dosage form, and strength of the proposed drug product are the same as those of the RLD except for any differences that have been the subject of an approved ANDA suitability petition. The applicant should reference the annotated proposed labeling and the currently approved labeling for the RLD. If differences exist due to the approval of an ANDA suitability petition, these differences should be delineated and a copy of the approval letter for the petition should be included.

Example format follows:

The conditions of use prescribed, recommended, or suggested in the labeling proposed for the generic drug have been previously approved for the reference listed drug. [Please refer to the labeling section for a comparison of (applicant's) annotated proposed labeling and to the currently approved labeling for the reference listed drug.] The active ingredient, route of administration, dosage form, and strength are the same as the reference listed drug.

A detailed comparison of the proposed drug and the reference listed drug follows:

	Generic Drug Product	*Downstate Clinical PET Center*
Conditions of use:	*FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*	*FDG injection is indicated in PET for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.*
Active ingredient:	*Fludeoxyglucose F 18*	*Fludeoxyglucose F 18*
Route of administration:	*Parenteral*	*Parenteral*
Dosage form:	*Solution*	*Solution*
Strength:	*6.8 - 35.7 mCi/mL*	*6.8 - 35.7 mCi/mL*

Under 21 CFR 314.93, a change from the RLD in strength, dosage form, or route of administration requires the submission of a suitability petition to obtain permission to file an ANDA with such a change. According to the Orange Book, the strength of the RLD for Fludeoxyglucose F18 ([^{18}F]FDG) Injection is 6.8 - 35.7 mCi/mL. The labeling of the drug product states that it contains 296 ± 3 mL of isotonic saline. Any change that affects the amount of the active ingredient or the concentration of the drug product (in mCi/mL) will be deemed to be a change in strength that, under 21 CFR 314.93, requires a suitability petition prior to filing the ANDA. Therefore, the use of a higher energy cyclotron may result in a more concentrated drug product for which a suitability petition is required under 21 CFR 314.93. In addition, a change in the total volume, and/or the amount of active ingredient, may result in a change of strength for which 21 CFR 314.93 requires a suitability petition.

E. Labeling

Refer to the *Fludeoxyglucose F18 Injection Labeling Guidance* and the Aug. 4, 1993, letter.

A side-by-side comparison of the container labels and package insert with all differences annotated and explained for the RLD and the proposed drug product must be submitted in addition to the four copies of draft (or 12 copies of final printed)

labeling (21 CFR 314.94(a)(8)).

F. Bioavailability and Bioequivalence

The applicant is required to provide information that shows that the drug product is bioequivalent to the RLD product upon which the applicant relies (21 CFR 314.94(a)(7)). (See also 21 CFR 314.94(a)(9)(ii) and (iii) and 21 CFR 320.22(b)(1).)

Any qualitative or quantitative differences in formulation from the RLD for parenteral drug products should be characterized and explained. A side-by-side comparison of the formulation of the proposed product and the RLD should be submitted. Analytical information and a physicochemical comparison should be included. Parenteral drug products may only differ in preservative, buffer, or anti-oxidant. If other changes are made in a parenteral drug product, an in vivo bioequivalence study may be needed.

Inactive ingredients used in the proposed generic drug product should have been previously approved in another drug product given by the same route of administration. The use of an approved inactive ingredient can be verified in the *Inactive Ingredient Guide*. The quantities of the inactive ingredient should not exceed the *Inactive Ingredient Guide* range. (Also refer to the *Interim Inactive Ingredients Policy* for information regarding exception and nonexception excipients.)

A waiver of evidence of in vivo bioequivalence may be requested for Fludeoxyglucose F 18 Injection. For certain drug products, such as Fludeoxyglucose F18 injection (abbreviated as [^{18}F]FDG), the in vivo bioequivalence may be self-evident. The FDA will waive the requirement for the submission of evidence obtained in vivo demonstrating bioequivalence if FDA determines that in vivo bioequivalence is self-evident. For example, in vivo bioequivalence may be self-evident if the drug product meets the following criteria:

- The drug product is a parenteral solution intended solely for administration by injection.

- The drug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application [21 CFR 320.22(b)].

Example of request for waiver of evidence of in vivo bioequivalence:

The (applicant) requests that the FDA waive the requirement for the submission of evidence demonstrating in vivo bioequivalence for (the proposed drug product). The

(drug product) meets the provisions of 21 CFR 320.22(b)(1)(i) and (ii).

In addition, under 21 CFR 320.22(e), for good cause, FDA may waive a requirement for submission of evidence of in vivo bioavailability if FDA determines that a waiver is compatible with the protection of the public health.

G. Components and Composition

Components (active and inactive ingredients) and composition of the drug product should be included. For Fludeoxyglucose F18 Injection, the active ingredient (drug substance) is Fludeoxyglucose F 18 (2-deoxy-2-[^{18}F]fluoro-D-glucose).

All inactive ingredients should be identified by their chemical names and their quantity and/or concentration (e.g., mg/mL) should be included. Applicants should refer to 21 CFR 314.94(a)(9)(iii) concerning the inactive ingredient changes permitted in a generic drug product intended for parenteral use. If inactive ingredients in the proposed product differ qualitatively and/or quantitatively from the RLD, information should be provided to demonstrate that the difference does not affect the safety of the proposed drug product. The submitted information should include, but need not be limited to, the following: (1) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and are within the same concentration range, (2) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (3) a comparison of the physical and chemical properties (e.g., pH, osmolarity, toxicity) of the proposed drug product with that of the RLD, and (4) information to show that the inactive ingredients do not affect these properties.

For [^{18}F]FDG, the Agency recognizes that the drug product formulated at the end of the synthesis (i.e., a batch) may be used as a single dose or as multiple doses. The quantitative composition of the unit dose may be assumed to be the same as that of the entire batch.

H. Raw Materials Controls

Information concerning the raw materials used for the manufacture of [^{18}F]FDG may be provided in the following format:

1. Components

    a. Name and Full Address(es) of the Supplier.

b. Method of Purification

If a component (e.g., mannose triflate, kryptofix) as received from its supplier is further purified or recrystallized, full information on this process, including the rationale, the method(s), and the solvents employed (if any) should be included in the application.

c. Specifications and Analytical Test Methods

For each component and inactive ingredient, the following information should be included:

i. The applicant should provide specifications and a test method for the identity of all components. The identity test should be performed prior to release of each lot of the material. Details of the analytical test method should be included in the application.

ii. If the suppliers of the raw materials are different than those listed in the RLD, then the suppliers should be validated. All raw material components should have acceptance specifications and be accepted with a certificate of analysis (COA). Full testing to determine the accuracy of the COA should be preformed. The supplier of the raw materials should be in compliance with Current Good Manufacturing Practice (CGMP) regulations. Once a supplier is validated, and a manufacturer wants to change suppliers, then the application should include data which demonstrates that the [^{18}F]FDG produced from raw materials from a new supplier are equivalent to the current supplier in terms of conformance with established specifications.

d. Retest Schedule

Each raw material should be retested periodically to determine that it still meets specifications. The periodic retest schedule should be provided.

2. Inactive Ingredients

For each inactive ingredient used in the drug product formulation, a statement

of its quality [e.g., American Chemical Society (ACS), United States Pharmacopeia (USP), National Formulary (NF)] should be provided. A certificate of analysis from a validated supplier that includes specifications and test results may be used to accept this material.

3. All Other Components (e.g. reagents, solvents)

A list of all other components which are used in the synthesis and purification of the drug product (e.g., all reactants, chemicals, solvents, reagents, that were not included above) should be included. A statement of the quality [e.g., American Chemical Society (ACS), United States Pharmacopeia (USP), National Formulary (NF)] of each component should be provided. A certificate of analysis, from a validated supplier, that includes specifications and test results may be used to accept this material.

4. Reference Standard

For [^{18}F] FDG, 2-deoxy-2-fluoro-D-glucose, a nonradioactive reference standard is used to establish and/or to verify the identity of Fludeoxyglucose F18 in the drug product. It also may be used for the determination of specific activity. The following information should be provided:

a. Source

Name and address of the supplier. If the reference standard is synthesized in-house, a statement to this effect should be included.

b. Proof of Identity

If the reference standard is purchased commercially, the applicant should include the certificate of analysis from its supplier. If the material is synthesized in-house, representative data to establish unequivocally the identity of the reference material lot as 2-deoxy-2-fluoro-D-glucose should be provided. The documentation should include complete spectrophotometric data, other applicable analytical data, as well as information on the synthetic route used.

I. Description of Manufacturing Facility

The following information should be provided (see also 21 CFR parts 210 and 211):

1. Name and full address(es) of the facility(ies) [including building and room numbers] used in manufacturing, packaging, release testing, and stability testing of the drug product. Please include the Registration Number of the facility.

2. Certification that the facility is in compliance with the Current Good Manufacturing Practices (CGMPs) (see also letter of Oct. 14, 1994, on field/headquarters agreement). The applicant and any contract facilities should provide the following statement with an original signature.

(Name of Applicant) certifies that the methods used in and the facilities and controls used for the manufacturing, processing, packaging, testing, and holding of (product) conform, and will continue to conform, to the Current Good Manufacturing Practice regulations under 21 CFR parts 210 and 211.

J. Outside Firms Including Contract Testing Laboratories

The following information should be provided:

1. Name and full address of each facility. Please include the Registration Number.

2. The function(s) of each facility.

3. A certification that the facility is in compliance with the CGMPs.

K. Manufacturing and Processing Instructions

1. Manufacture of Drug Substance

The following information should be submitted:

a. Batch Formula

The batch formula for the test batch(es) (e.g., the batch used in support of the application) and the proposed production batches should be included. A complete list of all the ingredients (whether or not they remain in the finished product) and their amounts used in the batch formulation should be provided.

b. Production of the Radionuclide

i. Description of the Particle Accelerator

A brief description of the particle accelerator including its make and model should be provided. Applicants should note that the validation information on the accelerator demonstrating that the equipment is capable of consistently operating within the established limits and tolerances should be available on site for inspection.

ii. Operating Parameters

Operating parameters for the production at the manufacturing site should be defined. Examples of the operating parameters that should be included are maximum particle energy, beam current, and irradiation (bombardment) times. The value(s) or range of values for each defined operating parameter should be included in the application.

iii. Target Body

Specifications for the target body and the foil(s) which come in contact with the target material should be provided. These should include the composition of the target body and foil materials and the volume of the target. Information should be provided on procedures which are used to establish equivalency when an existing target body and/or foil(s) are replaced.

iv. Recycling of Oxygen-18 Enriched Water

If oxygen-18 [^{18}O]water is not recycled, this fact should be so stated. If it is recycled, procedures used for its reprocessing should be described. Information should be provided to demonstrate that the recycling and/or reprocessing of [^{18}O]water does not change the drug product quality impurity profile.

c. Synthesis and Purification of Drug Substance

i. Description of Radiochemical Synthesis and Purification Equipment

The equipment used for the synthesis and purification of

Fludeoxyglucose F18 should be described. It should include a schematic flow diagram of the equipment from the target to the vial filling unit. A description of various components (e.g., tubing, reaction vessel, columns, and the function of each purification component (e.g., various columns) should be included. The components that are replaced after each manufacturing operation, and the components that are replaced periodically should be identified. Suppliers for each of the replaceable components (e.g., various purification columns and filter) should be provided. The procedures used in the assembly of components should be described.

ii. Description of Radiochemical Synthesis and Purification Operation

Identify the components and the processes that are under computer control and the ones that are under manual control. Applicants should note that the validation information demonstrating that the equipment is capable of consistently operating within the established limits and tolerances should be available on site for inspection.

A stepwise description of the radiochemical synthesis and purification operation, including in-process controls (refer to section L.), should be provided. An acceptable range of yields of the radioactivity for the drug product should also be provided. The proposed range of yields should be justified.

iii. Post Synthesis Operations

A description of how the synthesis and purification equipment is prepared for a subsequent batch should be provided. All cleaning and purging procedures should be fully described.

2. Manufacture of Drug Product

a. Production Operations

The procedures used in the manufacture of the drug product should be described.

b. Reprocessing of the Drug Product

A drug product batch should not be reprocessed unless the reprocessing procedures and conditions have been approved in the ANDA. If an applicant intends to reprocess a drug product batch, the conditions (circumstances) and full reprocessing procedures should be submitted.

c. Proposed Master Production Records [21 CFR 314.94(a)(9)(i)]:

A copy of the blank master production record, including a description of the equipment, to be used for the manufacture of a lot of the drug product should be included.

3. Microbiological Validation

a. Introduction

i. Purpose

The recommendations in this document apply to ANDAs for sterile [^{18}F]FDG. These recommendations also apply to approved applications when supplements associated with sterile processing are submitted.

ii. Documenting Sterilization Process Validation

Sterilization process validation data should be generated using procedures and conditions that are fully representative and descriptive of the procedures and conditions proposed for manufacture of the product in the application.

The Center recognizes that for most [^{18}F]FDG products, the final drug product will be manufactured using aseptic techniques rather than terminal sterilization. The Center also recognizes that conventional methods for the validation of aseptic processes may not apply to the validation of the sterile production of [^{18}F]FDG due to the very small number of product units manufactured from a batch or lot, and its short half-life.

Technical subsections of an application are often reviewed apart from the main body of the application. For this reason, it is

recommended that the microbiology subsection include an introductory description of the drug product (syringe, vial, glass, plastic, closure system) and the product's intended use. It is further recommended that the information describing sterilization processes be filed in a subsection (or volume) of the chemistry manufacturing, and controls (CMC) portion of an application. This permits the CMC subsections to be reviewed simultaneously by different reviewers in different locations.

b. Information for Terminal Moist Heat Sterilization Processes

It is not expected that FDG-F18 products will be sterilized by terminal moist heat processes. Information relating to aseptic processing for the manufacture of FDG-F18 drug products is provided under "Information for Aseptic Fill Manufacturing Processes" (section c.). However, should FDG-F18 be sterilized by terminal moist heat methods, information should be submitted in support of sterility assurance as described in Section II of the *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

c. Information for Aseptic Fill Manufacturing Processes

The following types of information should be submitted in support of sterility assurance for FDG-F18 manufactured by aseptic processing. The finished drug product should be described including the product solution (i.e., composition and pH) and the container-closure system(s) to be sterilized including size(s), fill volume, or secondary packaging. The route of product administration and the range of product dosage should be provided.

i. Buildings and Facilities

A brief description of the manufacturing building and aseptic facilities should be provided. The following information should be included.

- Floor Plan - A floor plan of the area(s) housing the aseptic filling facilities including preparation areas should be provided. The air cleanliness class of each area should be identified (e.g., Class 100, Class 10,000, Class

100,000). Isolators or barrier systems should be identified.

- Location of equipment - The placement of all critical equipment including, but not limited to, laminar flow hoods, autoclaves, and filling devices should be identified. Equipment within barrier or isolation systems should be noted.

ii. Overall Manufacturing Operation

The overall manufacturing operation including, for example, solution compounding, component preparation, filling, capping, and aseptic assembly should be described. The normal flow (movement) of product and components from formulation to finished dosage form should be identified and indicated on (or in relation to) the floor plan described above. The following information should be considered when describing the overall manufacturing operation.

- Drug Product Solution Filtration - The specific bulk drug product solution filtration processes, including the use of tandem filter units, prefilters, and bacterial retentive filters should be described. A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product. For simple aqueous solutions, a certification from the filter manufacturer is often adequate. Effects of the filter on the product formulation should be described (e.g., adsorption of preservatives or active drug substance, or extractables).

- Specifications Concerning Holding Periods - 21 CFR 211.111 requires the establishment of appropriate time limits for completing each phase of production to ensure the quality of the drug product. Therefore, specifications concerning any holding periods between the compounding of the bulk drug product and its filling into final containers should be provided. These specifications should include, for example, times, temperatures,

conditions of storage. Procedures used to protect microbiological quality of the bulk drug or components during these holding periods should be indicated. Maintenance of the microbiological quality during holding periods may need verification. These technical burdens may be reduced if components of the drug solution are prepared fresh each day and maintained sterile prior to compounding.

- Critical Operations - The critical operations that expose product or product contact surfaces to the environment (such as transfer of sterilized containers or closures to the aseptic filling areas) should be described. Any barrier or isolation systems should be described.

iii. Sterilization and Depyrogenation of Containers, Closures, Equipment, and Components

The sterilization and depyrogenation processes used for containers, closures, equipment, components, and barrier systems should be described. A description of the methods for validation of these processes should be provided including, where applicable, heat distribution, and penetration summaries, biological challenge studies (microbiological indicators and endotoxin), and routine monitoring procedures. Data (including controls) demonstrating distribution and penetration of the sterilant and microbiological efficacy of each process should be submitted. For applicants using drug product containers which are purchased sterile from a vendor, a certificate from the vendor may be provided to substitute for the above information.

- Bulk Drug Solution Components That are Sterilized Separately - If the bulk drug solution is aseptically formulated from components that are sterilized separately, information and data concerning the validation of each of these separate sterilization processes should be provided.

- Sterilization Information in the Batch Records - The batch record supplied with the chemistry, manufacturing, and controls section of the application should identify the validated process(es) to be used for sterilization or

depyrogenation of any container-closure components. This information may be included in the batch record by reference to the validation protocol or standard operating procedure (SOP), or by reference to the vendor certificate for drug product containers purchased sterile from a vendor.

iv. Procedures and Specifications for Media Fills

Media fills are simulated manufacturing operations using microbiological growth medium in place of drug product. The procedures and specifications used for media fills, and summaries of results for validation using the same container-closure system and filling process that is to be used for the product should be described. The microbiological testing method(s) used should be described. Any procedural deviations between the media fill and the production process should be indicated. A summary of recent media fill results (usually for at least 3 successful trials), including failures, should be provided.

v. Actions Concerning Product When Media Fills Fail

Descriptions of investigation plans and appropriate corrective actions should be provided.

vi. Microbiological Monitoring of the Environment

The microbiological monitoring program used during routine production and media fills should be described. The frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded should be included.

- Exceeded Limits - A description of the actions taken when environmental microbiological specifications are exceeded should be provided.

vii. Container-Closure and Package Integrity

The methods and results demonstrating the integrity of the microbiological barrier of the container-closure system should be

summarized. This should include testing for initial validation. For initial validation of microbiological integrity of container-closure systems, product sterility testing is not normally considered sufficient.

viii. Test Methods and Release Criteria

Product release tests for injectable products include sterility and pyrogenicity (or endotoxins) assessments as prescribed in 21 CFR 211.167(a). However, 21 CFR 211.165(a) permits the release of batches of drug composed of short-lived radiopharmaceuticals prior to the completion of sterility and pyrogen testing, but requires that such testing of each batch be started "as soon as possible." The laboratories performing these tests (particularly contract laboratories) should be identified and these should be in compliance with CGMP requirements.

- Sterility Test - Sterility test methods for [^{18}F]FDG will usually differ significantly from compendial test methods, so a clear description of the test should be provided. Procedures should be described and include the protocol for the selection of samples for testing. Testing performed within barrier systems should be discussed, and information concerning validation of the barrier system may be necessary.

- Bacterial Endotoxins Test and Method - Describe the bacterial endotoxins test for the product. This description should include qualification of the laboratory, inhibition, and enhancement testing and results, determination of noninhibitory concentration and maximum valid dilution. For further information see the agency guidance entitled *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*.

ix. Evidence of Formal Written Procedures

Evidence should be provided that there are formal, written procedures describing the above elements. Such evidence may

consist of standard operating procedures (SOPs), or a listing of SOPs or protocols submitted as part of the elements listed above.

d. Maintenance of Microbiological Control and Quality: Stability Considerations

Due to the extremely short period of use for FDG-F18, stability considerations with regard to microbiological quality are greatly abbreviated.

L. In-Process Controls

1. In-Process Controls

A description of any in-process controls should be provided. Examples of procedures that may be performed are the yields of fluoride ions (in mCi), temperature of the reaction vessel, gas pressure and/or flow rate, and synthesis time. In certain automated units, it may not be possible to directly monitor certain in-process parameters. In this case, it should be so stated.

2. Copy of Executed Batch Record

An executed batch record for a representative batch should be submitted. The following information should be included in accordance with 21 CFR 314.50(d)(1)(ii)(b):

- The specifications and test procedures for each component and for the drug product;
- Names and addresses of all facilities involved in manufacturing, processing, packaging, and testing of the drug product and identification of the operation performed by each facility;
- The name and address of the supplier of the container/closure system;
- The results (primary data) of any tests performed on the components of the drug product, as required by 21 CFR 211.165.

Applicants should note that although records for other batches (validation and/or stability) used to support the application, need not be included in the submission, additional information on these may be requested during the review process. Batch records for all the batches used to support the application should be available on site for inspection.

M. Labeling Procedures

The procedure for labeling of the drug product should be described.

N. Container

The following information regarding the container/closure should be provided:

- Name and full address of the manufacturer of the container/closure system or individual components. Appropriate DMF reference(s), if any, and the letter(s) of authorization (LOA) should be included in the ANDA;
- Container glass type (refer to USP chapter < 661 >); Composition of the stopper and crimp seal (e.g., aluminum);
- Physical description (e.g., size, shape, volume, product catalog number);
- Container/closure compatibility, including leaching
- Acceptance specifications and tests performed.

O. Controls for the Finished Dosage Form

For general information on controls for the drug product, refer to the *Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products*

1. Sampling Procedures

If multiple vials are manufactured, a sampling plan should be provided to assure that the test sample of the drug product is representative of the entire batch. However, if only one vial is manufactured, the description of the sampling procedure should be limited to the amount (volume) that is withdrawn from the final container and how it is distributed among the individual tests.

2. Regulatory Specifications, Methods, and Testing Schedules

The application should provide a list of specifications and identify the test methods (by name and code number) used to control the identity, strength, quality, and purity of the drug product. A schedule for performing each proposed test (i.e., pre or post release, frequency of testing) should be included. For [^{18}F]FDG, applicants should refer to section P "Analytical Methods" below for a list of tests that may satisfy the relevant identity, strength, quality, and purity criteria.

P. Analytical Methods

In this section, full details of the analytical test methods should be provided. The following is a list of tests and schedules which, in the current opinion of the Agency, satisfy the identity, strength, quality, and purity criteria for the drug product.

1. Appearance

The test method and specifications for the appearance of the drug product should provide insurance that the drug product is clear, colorless, and free of particulate matter. This may be accomplished by visualization of the drug product through leaded glass. If, due to radiation safety considerations, the ability to visually inspect [^{18}F]FDG is limited, one acceptable approach is to incorporate procedures to provide that: (1) each component or container-closure system is inspected individually for visual evidence of particulate, foreign matter, and container-closure defects immediately before use; (2) defective components will not be used; and (3) the batch production and control record of the [^{18}F]FDG includes a signed or initialed verification that such inspection was conducted and that only acceptable finished articles were used.

2. Identity Tests(s)

Test methods and specifications for the radionuclidic and radiochemical identity of the drug product should be described.

a. Radionuclidic

The radionuclidic identity should be established on every batch of the drug product by the method described in the USP monograph for Fludeoxyglucose F18 Injection.

b. Radiochemical

The radiochemical identity may be established by a chromatographic procedure by comparing the radioactive drug product with the well characterized nonradioactive 2-deoxy-2-fluoro-D-glucose reference standard in a procedure such as HPLC or TLC. The radiochemical identity test should be performed on every batch of the drug product prior to its release.

3. Assay (Radioconcentration)

Specifications (range), in mCi/mL, and the method of determination of radioconcentration of the drug product should be described. The method should clearly describe the procedure used for the determination of total radioactivity and the procedure used for the determination of the final volume in the container. This test should be performed on every batch of the drug product prior to its release.

4. Specific Activity

For [^{18}F]FDG, if a no-carrier added synthetic route is used, the specific activity need not be determined on a routine basis provided it is validated. Validation requires that the applicant of provide a drug product with consistent specific activity that at least meets the USP monograph requirements.

5. Purity

a. Radiochemical Purity

Specification and test method(s) for the radiochemical purity of the drug product should be described. A test method based on USP Fludeoxyglucose F18 Injection monograph may be acceptable. The radiochemical purity test method should be specific for Fludeoxyglucose F18. Applicants should demonstrate that the radioactivity associated with potential radiochemical impurities does not interfere with the measurement of radioactivity peak associated with Fludeoxyglucose F18. The radiochemical purity test should be performed on every batch of the drug product prior to its release.

b. Stereoisomeric Purity

In synthetic methods, where there is a possibility of formation of a stereoisomeric impurity (e.g., contamination of α and β anomers of fluorodeoxymannose in the electrophilic substitution synthesis method), a specification and a test method for the stereoisomeric purity should be provided. The drug product should meet the USP Fludeoxyglucose F18 Injection monograph for stereoisomeric purity requirements.

c. Radionuclidic Purity

Specifications for the radionuclidic purity and method for its determination should be described. The test method described in the

USP monograph may be used. With acceptable validation, the radionuclidic purity test may be performed after release of the drug product on the day of manufacture.

d. Chemical Purity

This drug product may be manufactured using different synthetic routes and processes and, therefore, may contain different impurities. Specifications, suitable methods, and schedules of testing for each impurity should be provided in the application. For example, if an applicant uses the Fludeoxyglucose F18 synthesis described by Hamacher et.al. [J. Nucl. Med. 27, 235-238 (1986)], then the residual amounts of kryptofix and the organic solvents employed in its manufacture may need to be monitored prior to the release of every batch of the drug product. Levels of other chemical impurities that may be found in the drug product (e.g., 2-chloro-2-deoxy-D-glucose) should be determined.

6. Pharmaceutical Quality

a. pH

A specification and the method of determination of pH of the drug product should be provided. The pH test should be performed prior to the release of every batch of the drug product. A pH paper test method may be acceptable, if performed using the reference standards at the lower and the upper range (with some allowance for the inaccuracy of the method) of the specifications. Applicants should note that during the shelf life, the pH of the drug product must remain within the proposed limits.

b. Osmolarity

Applicants should provide information that [^{18}F]FDG will yield a reproducible osmolarity.

c. Membrane Filter Integrity Test

The integrity of the membrane filter used to sterilize the radiochemical product should be assessed prior to the release of the drug product. The test method and specifications should be provided in the application.

The bubble point measurement method may be used to test the membrane filter integrity.

d. Bacterial Endotoxin Testing

The test should be performed on every batch.

e. Sterility Testing

The test should be performed on every batch.

7. Method Validation

The applicant should only submit those methods in the method validation package that are non USP methods.

Q. Stability of Finished Dosage Form[3]

1. Selection and Number of Batches

Where a 60 minute irradiation time is employed, a single stability batch will suffice. Where a range of irradiation times are employed, three additional batches of the drug product manufactured at the upper end should be studied.

2. Proposed Expiration Dating Period

An expiration dating period for the drug product, based on its stability, should be proposed in the application. The drug product should meet all specifications at expiry.

3. Test Procedures

Full testing should be performed at the initial time point (i.e., at release) and at the expiry period. Because of the short expiration dating period, the sterility and bacterial endotoxin testing need only be performed at release.

4. Storage Conditions

[3] The ICH Q1A guideline, *Stability Testing of New Drug Substances and Products*, and the *Guideline for Submitting Documentation For the Stability of Human Drugs and Biologics*(Stability Guidance) provide broad guidance in designing the stability studies for drug products.

Stability studies should be performed in the same container/closure system and at the same temperature in which the drug product will be stored during its shelf life (e.g., the drug product vial). The vial should be stored in the inverted position during the stability study.

5. Analytical Results on Stability Batch

The stability study analytical results should be provided in the application. Relevant information should include batch number, date of manufacture, storage condition, vial position, total radioactivity, and radioconcentration.

6. Postapproval Stability Protocol

The first three production batches are to be placed on the stability protocol. After the marketing approval of an ANDA, one production batch per year should be placed on the stability protocol.

R. Samples

If the analytical methods are to be validated in FDA laboratories, the applicant will be notified when samples should be provided. See also 21 CFR 314.94(a)(10) and 21 CFR 314.50(e)(1) and (e)(2)(i).

S. Other Information

Copies of cited references, their English translation (if not in English), and letters of authorization must be included as part of the other information in the application (21 CFR 314.50(g)(1) and (2)).

IV. REFERENCES[4]

Letters to Industry

October 31, 1986, letter to all NDA and ANDA holders and applicants on patent issues and the three-year exclusivity provisions.

[4]The reference documents are available from the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; (tel) 301-827-4573.

April 28, 1988, letter from the Director, Center for Drug Evaluation and Research, to all NDA and ANDA holders and applicants on the Drug Price Competition and Patent Term Restoration Act of 1984. The letter focuses on the three- and five-year exclusivity provisions.

July 29, 1988, letter from the Director, Center for Drug Evaluation and Research, to industry on the Drug Price Competition and Patent Term Restoration Act of 1984.

November 8, 1991, letter from the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to industry on improving the efficiency and effectiveness of the generic drug review process.

July 27, 1992, letter from the Deputy Commissioner for Operations to drug manufacturers/industry associations on the 1992 Generic Drug Enforcement Act, specifically on debarment certification and convictions statements.

January 15, 1993, letter from the Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to all ANDA and AADA applicants regarding refusal to file and refusal to approve incomplete applications based on the new requirements of the 1992 Generic Drug Enforcement Act.

August 4, 1993, letter from the Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to industry providing information on labeling, scale-up, packaging, minor/major amendment criteria, and bioequivalence requirements.

April 8, 1994, letter from the Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research, to all ANDA and AADA applicants on a variety of application-related issues. This letter also contains a list of industry questions and Agency answers resulting from the August 4, 1993, letter to industry.

October 14, 1994, letter from the Director, Center for Drug Evaluation and Research and the Associate Commissioner for Regulatory Affairs to all NDA, ANDA, and AADA applicants on the roles of CDER chemistry review scientists and Office of Regulatory Affairs field investigators.

Guidance Documents

International Conference on Harmonisation. 1994. *Stability Testing of New Drug Substances and Products*, ICH-Q1A, September 1994.

U.S. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) and Center for Veterinary Medicine (CVM). 1994. *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, November 1994.

DHHS, FDA. 1987. *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*, February 1987.

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DHHS, FDA, CDER, Office of Compliance. 1987. *Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices,* November 1987.

DHHS, FDA, CDER, Office of Generic Drugs. 1997. *Fludeoxyglucose F18 Injection Labeling Guidance*, January 1997.

DHHS, FDA, CDER, Office of Generic Drugs. 1994. *Interim Inactive Ingredients Policy*, November 17, 1994.

DHHS, FDA, CDER, Office of Management. *Inactive Ingredient Guide*.

DHHS, FDA, CDER. 1997. *Guidance for Industry: Organization of an Abbreviated New Drug Application (ANDA) and an Abbreviated Antibiotic Application (AADA)*, April 1997.